Environment and Resistance
in
Tuberculosis

A presentation of the nature of environment and resistance and their relation to the pathology, diagnosis, symptoms, and treatment of tuberculosis

BY

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ENVIRONMENT

Environment[1]

THE discovery of the tubercle bacillus made environment a new force in tuberculosis. Our surroundings took on importance according to their power to infect. An environment of dirt and darkness and overcrowding became an unfailing reservoir of germs and therefore of consumption; or, as an old saw put it, "Clean up your lung blocks and you'll clean up tuberculosis."

But with more understanding of the ways of tuberculosis came another view of the influence of environment. Not all denizens of our most notorious "lung blocks" fell prey to consumption. In fact, the greater number of them never showed a symptom of it, and lived to die of other things—of accident, of Bright's disease, of pneumonia, and what not.

Yet, as we learned new tricks, we found that nearly all these refractory subjects were tuberculous: they had tubercle bacilli in them and seemed to keep them. What then, we asked, makes a consumptive? Surely not mere infection with the

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right germs, for here are hundreds and thousands in just this fix, yet not down with illness. Again we called upon environment: it was environment which reacted upon some in a way that laid the body more open to the evil effects of their tubercle bacilli until the latter brought them low. As a catchword of tuberculosis etiology *environment* has earned a distinction second only to "nonresistance."

But what shall we understand by environment? It certainly does not mean the same thing to all men. Perhaps its scope cannot be strictly defined; no doubt, too, there is no general agreement as to its scope. To various men it will convey an impression of larger or smaller domains.

Not long ago I got to discussing the causes of tuberculosis with several men who are in the forefront of our work. After a good hour's interchange of ideas it became plain that each of us cherished his own concept of what comprised environment and that no two notions coincided at all points. I was then told what was really altogether new to me. This was that to a large number of our most active and most competent antituberculosis workers environment from beginning to end meant nothing more than those physical objects which encompass human beings—more concretely, the cities, the streets, the houses and backyards, the rooms in which we live and move, the baths, the windows, the stoves, the furniture, the clothing, the space, air and sunlight which people may or may not have. I learned that there was a certain aggregate of all this gear

which made up a standard of what is called good hygiene and that a falling short of the standard spelt poor hygiene. I heard further that not a few public health workers believed that if good hygiene, as I have outlined it, were brought to pass and were kept up, tuberculosis as a disease would be checked. And, in answer to my inquiry as to who believed this, one or two eminent names were cited.

Now everyone would admit that a thorough cleaning up of our physical environment would in time bring about a disappearance of tuberculosis, simply by removing all chances of contact with tubercle bacilli, even though no other influence were exerted upon us. But I take it that this evening light is desired, not so much on how environment may establish or do away with opportunities for infection, as on how it may convert a well though infected man into a sick one or promote those conditions which permit infection to assume a more or less progressive course. Our task is to discover whether environment is in any way responsible for the circumstance that many tuberculous persons fall ill though most remain in health. And, in examining environmental factors, we must of necessity pay attention to such purely external surroundings as we have just named.

Yet surely, for our present purpose, this is much too narrow a view to take of environment. There may, for instance, be an environment of disease—of measles, of septic infections, of the common cold, of influenza, to mention only a few. If asked

whether this type of environment is not of necessity bound up with that of conditions of living and housing, we would answer in the negative: for the recent pandemics of influenza, with their frightful toll throughout the world and among all types of civilizations and societies, make it impossible to view this particular scourge as decisively influenced by any habits and modes of living that we are familiar with. Measles is of the same piece.

Again, altogether apart from an environment which is to be comprehended under good hygiene, there is an environment which would comprise numberless opportunities for physical injury to the person. This would include many perfectly accidental happenings, the normal hazards of human association, which neither foresight nor law nor instruction can do away with wholly.

There is, besides, an environment of occupation. The man at the desk or counter, the shoemaker, the tailor, the glassblower, the cabdriver, the farmer, the athlete, the peddler, the miner,—all have the physical marks of their work upon them. The life, the customs, the habits, the demands and necessities of the several classes of society leave their traces on their members no less. If we compare the peasant girl with one gently bred, at age sixteen, we not uncommonly find no differences in health, grace and beauty; or, if there be a difference, the comparison as often as not favors the former. Yet how often have we seen two or three decades of rough, country life, ever vaunted as the road to health and content-

ment, make of the one a broken woman, old before her time, while the same period of ease and urbane existence bring to full flower all that was budding in the maiden.

When, sick with angina pectoris and aware of the influence of psychic disturbance upon his physical condition, John Hunter said that his life was in the hands of any rascal in London who chose to take it, he simply indicated the possible more disastrous effects of an environment about which our books on general medicine are strangely or perversely silent, yet which drives thousands of us mortals to our practitioners. This is the environment of personal association—of antagonistic personal association, in particular. The older philosophers and brooders over our well being were enormously impressed by this factor in human nosology: dust off again your old Burton and read how it appeared to him. Yet, for a considerable period, until recently, when psychiatrists again brought this type of environment into prominence and coined a new nomenclature to speak intelligibly to one another of "repressions" and "conflicts," and the morbid results of these, formal medical instruction, given to more material and mechanical views of disease, was apparently oblivious to its existence and influence.

It should hardly be necessary to point out the enormous amount of functional disturbances which the reactions of jarring personalities bring into being: nor are their effects on already established organic

deficiency or disability any less marked. Every physician soon becomes familiar with them and is mindful to attempt to control them when treating his patients. There is a social and family environment of amiability and good fellowship and contentment and happiness: it may exist in surroundings which physically may be far from our accepted hygienic ideal; and its effect on the general well being of those happily situated in it is all good. This much is, I think, beyond dispute. But there is also a radically different environment: one of incompatibility, and oppression and brutality, and even bestiality. It is by no means the heritage or appanage of the hovel exclusively. It may dwell where air and space and light and food leave nothing to be desired; yet even here it will make for ill health.

It is a statement, worthy at least of debate, that the fullest development of the race requires those conditions—that social and political environment—which will allow the greatest freedom and play of individuality. It is nevertheless a commonplace, a criticism in fact, that one great weakness of all plans for ideal commonwealths, from Plato's system down to the actual feeble shadow of democracy today, is a certain insistence that all men conform to common standards. Out of this struggle between the instinct and passion for self-expression, on the one hand, and those rules and standards of conduct which, on the other, society deems necessary for its own fixity and security, innumerable conflicts

arise. The issue of these may be acquiescence: all educational systems teach the child docility with the decalogue and society is never lavish with its fleshpots to the fractious colt. But only too often their ultimate results are what we call misfits, or the apathy of despair, or, occasionally, even self-destruction.

In and by reason of all this welter, not a little physical ill health emerges. Concerning still another side of this phase of environment, that so ardently played up by Freud and his followers, I think that little need be said here, though I recognize much that seems valid in their contentions.

I would not overemphasize the part played in disease by disturbances of the psyche. I wish merely to point out that it is a very real influence, arising out of what is almost man's normal environment, whether this be made up of relationships that exist between him and his kindred or those between him and more casual associates or the ideals and practices of society at large. I do think that to deny its influence on health is to disregard some of the most obvious phenomena that confront us.

I need not give a more detailed recital of what enters into my own comprehension of environment. The long and short of it is that environment comprises everything and all things that enter into the experience of a human being; and that, as regards tuberculosis, any experience that may modify in

any way the origin and development of infection is an environmental influence.

Perhaps this view is too all-inclusive. It would, for instance, make malnutrition an environmental factor, unless in any particular case malnutrition were the result of inborn tissue or organic vice, and not of deprivation of necessary food elements or improper ingestion or absorption. Yet, under the latter circumstances, malnutrition is assuredly as much an affair of environment as is the nature of the house one lives in.

At any rate, too great inclusiveness will undoubtedly lead to less misunderstanding than too narrow a point of view. As I see it, only two really fundamental factors can possibly have an influence on infection or disease. These are heredity and environment. Inheritance determines the nature and activities, whether these lie fallow or are at any or all times fully expressed, of the tissues as these are born into the world. Environment includes every mundane experience which, directly or indirectly, may exert an effect on the constitution and function of tissues.

There are only two ways in which clinical tuberculosis can develop. These are—once infection takes place—through the advance or renewal of activity of foci which have existed, perhaps unknown to their possessor, for variable lengths of time (theoretically, the period may be almost as long as a lifetime itself); and through the uninterrupted

progression of foci from the time of infection to the cropping out of symptoms.

Cases of the first type are common: many are comparatively easy of demonstration. We meet with patients whose breakdown is of the nature of a clinical relapse. It may be a first relapse or a third or fourth recurrence of symptoms, coming on after perhaps years of good health and working capacity. Examination of them may disclose that the particular breakdown is due to renewed activity of foci which were known to exist and give rise periodically to symptoms before.

Or, as happens often, patients at the very first manifestation of symptoms of tuberculosis are found to have morbid changes which, because of their character and extent, are beyond question the culmination of years of quiet infection. Here again we are satisfied that clinical disease is the result of infection received much earlier in life. Generalized miliary tuberculosis and acute tuberculous pneumonia in previously healthy adults invariably spring from an extension of infection from preëxisting concealed and quiescent foci: as do primary clinical tuberculosis of bones and joints, kidney, pleura, peritoneum and brain membranes. The frequency of clinical relapse plus the frequency of primary symptoms of tuberculosis of the lungs with old and extensive infection plus the frequency of clinical tuberculosis first appearing in organs without direct communication with portals of entry is proof enough that very, very often clinical breakdown is

not the expression of recent infection from without but is the effect of renewed activity or extension of long dormant tubercle.

Whenever anyone asks me why, in general, these cases break down, I am accustomed to answer that there are many immediate, potential contributory causes which are often demonstrable and to which I shall refer in a moment. But over and above all cases in which the sequence of events is plain, careful and practised observation of patients and cadavers will bring to light not a few in whom we must conclude that the catastrophe happened because of purely fortuitous and accidental circumstances. The term *accidental* may be unscientific; yet I know of no better way to put the case, which is this—that, as regards such elements as the focalization of infections and the influence which extraneous factors may exert upon them, there are accidental circumstances of place and time which may be, which I have no doubt are, decisive in moulding the subsequent turn of events—for better or for worse so far as the patient is concerned.

I take up these accidental factors of etiology and pathology and their results at greater length in the essay on *Resistance* and shall not dilate upon them here. But I may be permitted to repeat that altogether apart from other factors, such as dosage of bacilli, resistance of host, etc., the actual point of localization of even the primary infection may be of great moment. A focus in immediate proximity to a large vein or the thoracic

duct must, with everything else equal, certainly be regarded as pregnant with greater evil than one at the very lung apex or a lymph node in the mesentery. We cannot conceive that any element of inheritance, resistance, virulence, or *ordinary* environment, as the latter is understood, was responsible for focalization in the one place rather than in the other, or contributed to the event in any way. There were of course some environmental factors of tissue relations and activities, operating at the time, which did determine the exact point of focalization: but these are hardly ever demonstrable and are far beyond the scope of my analysis. We can only say that in some instances the place of focalization was accidental and let it go at that.

But note how decisive it can be. The focus in apposition to the thoracic duct may ulcerate, to spread generalized miliary tuberculosis and death. The ulceration of a similar focus in a lymph node of the neck would eventuate in a comparatively benign condition.

If we keep alert and receptive, we can get our best lessons in the etiology of clinical tuberculosis from the sufferers themselves. Their stories, told daily in consultation rooms, and our observations, gleaned at the bedside, proclaim again and again the immediate causes of breakdown, and to me far outweigh any evidence, positive of otherwise, to be gained in any other manner. I have lately read several contributions in which the authors report that they have examined the histories of soldiers who developed

tuberculosis while in the army, have cast up columns of figures and have found that none of the tuberculous soldiers had received wounds that bore any relation to their tuberculosis. Or they have gone into certain more or less complete records of the wounded and have discovered that no tuberculosis struck down these men later. In either event, they conclude, therefore, that trauma, injury, does not bring about clinical tuberculosis.

Now it may have been perfectly all right for these authors to tell us that none of their cases developed tuberculosis because of trauma, but to say that trauma has no influence on tuberculosis is a totally different matter. It may not in most cases: or the association may be difficult or impossible to detect. But it does have an influence in some cases: and we should remember that, when it comes to the complete affirmation or negation of a general principle, a single positive phenomenon or finding will completely outweigh all negative reports, no matter how overwhelming appears the numerical evidence against. If Claude Bernard had announced his discovery of glycosuria by *piqûre* of the fourth ventricle immediately after his first experiment and had rested it there, any number of followers in his footsteps would have no doubt convicted him of error if this depended on statistical evidence. For, before he made a second sucessful *piqûre*,—until he discovered the exact spot where *piqûre* always aroused glycosuria,—the discoverer himself had almost a score of failures. It would probably not be difficult for

some surgeons of large experience to prove numerically from their own records that cancer never arises from gastric ulcer: in observing hundreds of cases of the latter they had never encountered cancer. Yet an obscure country physician may find that his only case of ulcer of the stomach was changing into cancer. I have heard some sweeping generalizations about the nonoccurrence of pulmonary tuberculosis with mitral stenosis; yet I have observed this coexistence of diseases. Not long ago, a physician brought to me a patient who fell ill with acute pleurisy with effusion not twenty-four hours after an injection of tuberculin. The injection was one of a series given the patient in order to determine the nature of an affection of the eyes: the pleurisy with effusion was her first pulmonary "episode." The physician in question had previously administered tuberculin hundreds of times for the same purpose and always without untoward result. Before the excitation of this pleurisy, I have no doubt that out of the fulness of his experience he would have been willing to have written a paper to the effect that tuberculin, as he gave it, would never provoke clinical tuberculosis.

I once saw a man who recovered health in a sanatorium and returned, a well-arrested case, to follow his occupation as a chauffeur. He remained well; until, one day while bending over to crank his automobile, the crank flew off and struck him a violent blow on the left side of the chest where he had had active tuberculosis. He at once be-

came very ill and was found to have sustained a pneumothorax.

In this case there cannot exist the slightest doubt about the influence of trauma. It immediately ruptured an already diseased pleura. I have observed hemorrhage to follow a blow on the chest and, after the hemorrhage, acute pulmonary tuberculosis which was beyond question the first breakdown that the patient had ever experienced. And this patient, at first examination, was found to have an entire lung involved with old, sclerotic tuberculosis and a cavity at the apex. It is not to the point to ask why she did not break down before. What is significant is that an injury precipitated her clinical tuberculosis. In a phthisical billiard player I have seen a remarkable warty tuberculosis of the skin, growing between the thumb and index finger of the left hand, in the crotch where the man was accustomed to rest and move his cue.

In my opinion, there is not the slightest doubt as to why tuberculosis manifested itself in the manner, both as regards time and place, described in these three cases. We can unhesitatingly affirm that had trauma not been applied, symptoms would not have occurred *when and where they did.* They are all striking examples of environmental influences on tuberculosis. Trauma does bring tuberculosis to light—so much is certain. As to what proportion of breakdowns is attributable to trauma is another matter, which need not concern us here.

At this place it may be well to consider for a moment the influence of pregnancy, labor and the puerperium. There is not a single physician, be he obstetrician, phthisiologist or general practitioner, who would believe for an instant that the gravid state and its sequellae have no effect on tuberculosis. By far the greater number of women, of course, go through this experience without exhibiting the least evidence of tuberculosis. But we do not draw our deductions from negative data; and the fact remains that the proportion of tuberculous women whose breakdown was ushered in by pregnancy or childbearing is still lamentably high.

I know of no better examples of the direct influence of what we may call noninherited factors on tuberculosis than pregnancy will now and again afford. Consider the following case: A young woman, gently reared and always vigorous and athletic, bears a child, and has a protracted convalescence in bed, with pleurisy with effusion, which develops soon after delivery. She recovers completely and outwardly remains in good health until the birth of a second child, when she breaks down with acute tuberculous pneumonia.

Or this second case: A perfectly healthy woman becomes pregnant, bears a child, and is then confined to bed for an unusually long time because of indefinite symptoms of illness, although she has some cough. She recovers after a while and two years later has a second child; and, this time, during the puerperium she again has cough and fever, and now spits blood.

Once more she recovers, and several years later bears a third child, a short time after which she has profuse hemorrhages from the lungs and falls into acute pulmonary tuberculosis.

Every physician could multiply such cases at will. In many of them there can be no question about what caused the breakdown. We can be perfectly certain that an environmental factor, speaking broadly, turned the balance against a continuance of quiescence of infection. We are no less sure that feeding or inherited qualities, or other factors of environment, such as housing, etc., either had nothing to do with the event or, if they did, they played completely subsidiary parts. The one outstanding fact is that the patient broke down at this time because she became pregnant and bore a child and that, if she had not had this experience, there is not the slightest reason to believe that she would have developed clinical tuberculosis at the time.

Acute infectious diseases, particularly those which may cause disturbance of the lymphatic or respiratory system, are very frequently determinants of the outbreak of clinical tuberculosis. Measles, the common cold, influenza, septic infections (especially of the throat), are some of our most notorious "whippers-up" of tuberculosis. We are familiar with the harmful effect which a cold may exercise on a patient who is being treated for tuberculosis and who, before coming down with the cold, may have been making satisfactory progress toward

arrest of his lung trouble. We are similarly impressed by the large number of patients who break down with tuberculosis for the first time after contracting a cold or an acute bronchitis. In both instances the same interplay of forces is undoubtedly at work: foci which had attained fairly competent investment, and thereby relative quiescence, participate in the congestion brought about by the inflammation of an added acute infection and are thus stimulated to fresh activity. Measles may bring about the same result, especially in the lungs and lymph nodes; and, as is well known, may in addition profoundly depress the allergy of the body to tubercle bacilli. So may influenza.

Physical and mental overstrain and excesses of all kinds promote tuberculosis. Their action is well understood. Their results are so frequently encountered in patients that little room is left to question their part either as contributory or decisive environmental factors. We meet with the spectacular case,—the vigorous athlete stricken with pulmonary hemorrhage immediately after finishing a race. We listen to the stories of gradual let-down in health and insidious encroachment on working capacity, through months and years of overwork or worry or wrong living. And there is every type of onset in between these two.

During the past decade or two our point of view concerning the influence of crowded and unsanitary living conditions has shifted considerably. I have said that at first it was believed that opportunities

for infection played the decisive rôle in tuberculosis morbidity. It was then thought that relatively much disease developed in the tenements because the condensation of population and its attendant evils established quantitatively an unusual measure of contact with tubercle bacilli. But, as it became more and more apparent that adult breakdown was a frequent consequence of early and long-standing infection, newer explanations were demanded.

These explanations are not far to seek, and are in general much more rational and no doubt nearer the truth than was the older quantitative infection idea. The evils that create and accompany sub-standard living arrangements—poverty usually, with its overcrowding, filth, darkness and deadness of air—are plain and need but slight elucidation. People who live in an environment of this kind, with few of the comforts and more refined interests and pleasures of life, overburdened only too often with children, are exposed to all the stresses and deprivations that result from this mode of life—improper or insufficient food and clothing and heating, irregularity of *ménage*, overwork, deprivation of the recreative enjoyments with excess of those that are dissipating and vicious, unusual opportunities for contact with many acute infections, lack of proper aftercare in pregnancy and disease, etc. In short, such an environment is our most fertile soil for the development of conditions which go far toward undermining and breaking general health, and thus lay the train for the lighting up of quiescent tubercu-

lous infection and bringing it to clinical appreciation. As standards of living go down, ignorance, squalor, exposure to cold and heat, hunger, lack-lustre discouragement and indulgence of bestial appetite increase apace. And one general result can be nothing else than a deterioration of health.

In every part of the world comparative statistics of tuberculosis have always shown two outstanding relations. The curves of illness and of death from tuberculosis have always run parallel with those of general disease and mortality, and opposite to the economic status of a population or any section of it. The only time when the second relation was not apparent was during the world war when, with whole nations deprived of many essentials of normal living, modes of life did not accurately reflect economic status.

But, normally, it invariably follows that high general morbidity and death rates will be accompanied by high tuberculosis rates of both types, and that where poverty prevails there tuberculosis will be high and *vice versa*. These facts furnish the most compelling brief for the positive argument on the influence of environment on tuberculosis.

We have thus far been concerned with marshaling an array of factors, all of which are to be looked upon as environmental, which must be taken into account whenever tuberculosis breakdown on the basis of preëxisting infection comes into question. If we be required to bring forward direct evidence of the

influence of environment and, further, asked to explain its *modus operandi*, we would, first and above all, go to therapy to demonstrate our thesis.

There can be no dispute over the general proposition that the intelligent application of what we call hygienic-dietetic treatment will improve the condition of most tuberculosis patients. The better informed opinion also recognizes that the most effective element of this regimen is the limitation of the patient's activities—a relief from responsibility and stress which is so prescribed as to meet the individual patient's needs and capacities. The therapy of chronic maladies will provide few more striking examples of functional betterment than that occasioned by the judicious use of rest in circumscribed (nongeneralized) tuberculosis. Under its influence the consumptive to whom, while active, every step was painful with fatigue and every small task appeared almost insuperable labor, finds his whole outlook changed. Put him to bed or fix him to his chair, and he becomes comfortable, his fever and too rapid pulse tend to decline, distaste for food abates and he puts on weight—all this, very often, with astonishing rapidity. A glance through sanatorium reports will show that this is the *institutional* history of fully three-fourths of all patients. And there can be few men, of those familiar with the handling of the tuberculous in our sanatoria, who have not often thought that if the average time of discipline could be lengthened from less than six months, as it now is, to say three years, our ultimate

arrest and mortality figures would be completely reversed.

We are, of course, speaking now of the ordinary sanatorium patient—not the *phthisicus in extremis*. And, in this connection, close observation of the physical powers of individual patients is highly significant.

While at complete rest, many may be altogether without symptoms. Or, if at rest most of the day, they may even be able to indulge in some activites—walking, for instance—for fifteen minutes, an hour or two hours a day, without functional disturbance. Every phthisio-therapeutist comes to learn the physical limitations of his patients, of each individual one of them. He finds that a man who, at a given time, may be able to do fifteen minutes' exercise, will suffer if he exceeds this; or that another patient who may go through a whole day of light work comfortably will have his symptoms return if put at heavier tasks; or that some who have been practically well for months can be "broken," as it were, if made to do unusual labor.

This simple and common clinical experience, available to all who wish to make the experiment, proves, better than all other evidence, that environment does have an influence on tuberculosis—an influence, powerful though delicate, and ever active. The constitutional symptoms of tuberculosis are put in motion by the action of substances that are absorbed from foci of disease. The rate and amount of this absorption are contingent upon the character

of the foci on the one hand and the physiological activities of the tissues which enclose them on the other. The character of the foci at any time is largely the net result of antecedent experiences on the part of their possessor: we may, for instance, alter them at will by certain manoeuvres in animals of experiment. The physiological activities of circumtubercular tissues vary, like those of any other tissues, with the experience of the individual—the experience, which is, of course, the play of environment upon the person. Physiological stresses and disturbances are set up by environmental conditions of many kinds, whether these be physical or emotional overstrain, or disease in general. Disease is undeniably related to occupation, to position in life, to personal association, to living conditions, and what not. It produces many physiological effects—changes of respiration, circulation, digestion, metabolism, etc.—which are not to be distinguished fundamentally from those due to abnormal physical and psychic activity.

At any rate, if environment has no effect on treatment, we may just as well give up our present methods and turn our patients loose to follow their own inclinations and take their chances with the tissue stock that was born with them. Even then, some would regulate their activities so as to create for themselves an environment such as we prescribe. For men suffer when they have tuberculosis. To many such, activity becomes painful—painful to the point of impossibility to indulge in it. And thus

slowed up, they would seek rest; when not a few would pull through, or experience periods of relief—those delusory periods which so normally punctuate the natural history of tuberculosis, the seasons of the "false convalescence" of Laennec, which quacks and nostrum traffickers have learned to exploit so well.

If, however, environment does influence tuberculosis as we encounter the latter in treatment, then it must also have its effect in contributing to breakdown. Any other view is irrational. If the influence of environment is so delicate that a few minutes' more or less walking means much to the focus which is, as it were, sensitively balanced, its influence on quiescent, latent or concealed foci is no less delicate. True, in the latter case it may not be so eloquently expressed, if the environmental force remains quantitatively small. A quiet walk of half an hour would undoubtedly not have produced the least visible effect on the young athlete I knew, who had his first manifestation of tuberculosis—a haemorrhage—immediately after finishing a half-mile run and who is now dead after a prolonged illness with tuberculosis. But relations here are largely those of quantity. The mechanism of going into breakdown, or relapse, or transient or prolonged increase of activity is not very different fundamentally. The sum of the effects of environmental forces reaches a totality which the balance between foci and surrounding tissues can no longer withstand.

There remains another angle from which we may discuss environment as a factor in breakdown from tuberculosis.

It will be admitted that the presence of tubercle bacilli in one's surroundings is a very real environmental factor. It will also be agreed that this bacillary environment is very variable in quantity and character of bacilli and in the media that contain and transmit bacilli. If, therefore, future observation and investigation should disclose that the repeated or continued attachment of these germs to human beings promotes in many instances the outbreak of clinical tuberculosis, the nature of one's environment would on occasion play a very decisive rôle in determining the issue of infection.

During the last decade we have become perfectly certain that an initial tuberculous infection endows an animal with increased resistance to reinfection from without (and, as a matter of fact, also from within). At the same time it has become common knowledge that the postpuerile ages of man are pretty thoroughly infected.

Out of these two circumstances has evolved the opinion, which in some quarters has hardened almost into dogma, that reinfection is impossible if a person has once been infected and that *all* manifest tuberculosis after childhood develops from infection acquired by the time adolescence is established.

Future work may show that all this is indubitably true. But I have never been able to convince myself that the evidence at hand warrants the

assumption of either proposition as a generalization of fact.

The idea of the impossibility of human reinfection has been based on work contributed from the laboratory. Yet no experimental work that I am familiar with has made as sweeping a statement as that an infected animal cannot be reinfected. Indeed, the facts of the matter, the all-important details of controlled experiment on animals, point all the other way.

It is true that primary infection of animals confers a high measure of protection against reinfection. But at no time is this ever absolute: sufficiently large doses will break it down. We also find that even moderate or small reinfections are always met by the animals with some kind of tissue response (morbid change). Some type of tuberculosis never fails to result, even though this be modified. It is not the progressive tuberculosis that results from the same dose of a primary infection, to be sure; but it is tuberculosis none the less; and I have seen it persist for a long time.

In other words, the net immunizing effect of primary infection is not so much a flat and complete protection against reinfection, as it is a change of type in the tuberculosis which follows reinfection. In a susceptible animal, a first infection, properly applied, is apt to spread rapidly throughout the body and take on a progressive character. On the other hand, reinfections of the same animal, if dosage be small, tend to remain well-localized at the place of

infection and pursue a much more sluggish and chronic course. The more ordinary clinical tuberculosis of human adults resembles in several important features the reinfection tuberculosis of laboratory animals. As a matter of fact, there is just as much evidence to indicate that it may at times represent reinfection from without as there is to urge acceptance of the doctrine of nonreinfection from without.

Cattle immunization has given us much of our best information concerning immunity to tuberculosis. The type of primary infection that results in the process of active immunization is also most comparable to what presumably occurs in the generality of mankind; that is, in cattle it is aimed to attain a self-limited, well controlled infection, such as usually takes place in human beings under natural conditions.

Yet it is under these very conditions, that is, when primary infection in nonprogressive, that we find immunity to outside infection to be less high and less permanent. All cattle immunizers have found, for instance, that, even after a vigorous course of protective inoculation, a satisfactory defense against virulent reinfection cannot be maintained for much longer than two years. In summary, the results of investigations on cattle and other animals have turned out about as follows: (1) primary infection confers protection against reinfection; (2) the protection is not complete; (3) as the primary

infection tends to die out, as it will unless it progresses, the protection diminishes or disappears.

Much more might be said about other more or less decisive features of immunity; as, for instance, periodic anergy. This, a depression of resistance to a point below even that which is native or normal to an animal, occurs in the course of every immune process and is brought about transiently, by new infections similar to or different from the one which an animal may be harboring at any time. It has, received little experimental study in connection with immunity and has thus far been almost entirely lost sight of in all applications of allergo-immunology to human tuberculosis. But I think I have said enough to indicate that the dictum that the average human experience is a single early infection with tubercle bacilli is, to say the least, highly debatable.

The whole matter of human infection must be subject to vastly more complexities than many have assumed. Manifold opportunities for infection exist: this much is certain. Between milk and crude sputum and dust and consumptives and the articles the latter handle, that person must be rare who moving in ordinary society, does not come in contact with tubercle bacilli, not once or occasionally, but frequently and repeatedly. There are, for instance, many habitations in our cities, where children, living in one or two rooms with careless, phthisical parents, must for months ingest and inhale tubercle bacilli almost continuously. There must be others who, fed tuberculous milk, ingest enormous numbers of

bacilli throughout a long period. They do this in health and in sickness; when allergy (immunity) is high and when, as for example during other acute infections, it is low or absent.

There must also be many whose contact with tubercle bacilli is quite transitory; and not a few whose initial infection is extremely slight. I cannot go into the matter of the complete healing of tuberculous changes here, other than to say that they do disappear entirely, as the later developments of tuberculous peritonitis of man have frequently disclosed, and as cattle inoculations have shown. And, until the contrary is definitely proved, we must assume—at least, we cannot deny—that many initial human infections, if slight, are transitory, and that, upon their thorough obliteration, immunity dies out, or is so slight that the possessors are as open to reinfection as though they had never before come in contact with tubercle bacilli.

Earlier in this address I tried to make plain that breakdown on the basis of old persisting infection comes very frequently into the practice of every physician. But, at the present moment, I cannot convince myself that this type includes all or most cases of manifest, adult tuberculosis. In view of the immunological details which I have just mentioned and also because of the varying opportunities for infection that obtain outside, I cannot help believing that the everyday life of man provides conditions that make for a not inconsiderable number of

tuberculous reinfections from without, in which the time and quantity of reinfection may be so ordered that, because of these, breakdown results. I do believe, therefore, that, in this respect also, environment may play a decisive part in the development of disease.

But environment is not the only force that hurries a man into tuberculosis or wards it off. Inheritance must also play its part. The little that we know about specific immunity suggests that at some future time it will be found that a cumulative ancestral experience with active tuberculosis transmits an increased resistance to the progeny. But how much this more resistant tissue stock may be balanced or outweighed by environmental relations, such as greater opportunities for infection from phthisical family associates and the reduced economic conditions that follow in the train of consumption in a family, is a question for argument and investigation.

There is not a little clinical evidence that such diseases (to mention only a few) as gout, epilepsy, migraine and cardio-renal-vascular insufficiency arise on an inherited background. It has always been a byword that longevity is inherited. Nervous instability and overirritability certainly are. And who knows but that nervous irritability, which at bottom must regulate cellular activity in general, will not ultimately be found markedly to influence the origin and development of infections?

But I am not here to discuss inheritance. I merely throw out these hints as matters to be thought of, and to emphasize that a narrow view of the causes of the development of phthisis is unscientific and not justified by facts or probabilities.

RESISTANCE

Resistance[1]

AS OUR insight penetrates deeper and deeper into recesses that were once dark to us we consciously or unconsciously demand more precise description of terms to denote phenomena that obtrude upon our senses but defy our understanding. Upon first appreciating a thing, be it light or sound, an abnormal sensation or an unusual conformation of the body, we give it a name. But we are mentally so endowed that we are not long content with the mere name of a thing. We must know where and how it begins and ends, and through what media it works. We must discover its attributes and, these made plain, we must enlarge and refine our definition and description. As the latter grow more exact there comes the perception that nothing that we sense is isolated or spontaneous. It is born of something and brings forth something. And, once our minds begin to deal with its causes and effects, then we can say that the thing has entered our understanding. Then only can we affirm that its name is to us perhaps something more than a mouthful of words.

[1] An elaboration of an address, "The Nature of Resistance to Tuberculosis," before the New York Academy of Medicine, February 15, 1917, and published in the *American Review of Tuberculosis*, April, 1917. Material from a number of the author's other papers on "Resistance" and related subjects has also been included.

Terminology, description and comprehension of cause and effect: every domain of knowledge, every phase of science passes through these three stages on the road from sensation to reason; and medicine, focus of all sciences, embracing all, taking of and using mathematics and physics and chemistry and botany and climatology and sociology and psychology, is to-day perhaps in all three stages. A genius, a Helmholtz, emerges and lays bare the mechanism of the eye. A Richard Bright, a Louis or a Gerhard sifts and describes and clarifies a confused mélange. A man with a knack for observation, perhaps a dermatologist, classifies those things that are red, or those that are raised, or those that itch, or those that are wont to appear on certain parts of the body; and he thereby brings into order his "science" and takes a step far beyond the time when he called everything either a humor or a tumor. But terms, mere terms, persist, and too often pass for explanations. Nephritis, cardio-nephritic, myocarditis, arteriosclerosis, hypertension, hypertensive-nephritic, myocardial insufficiency with hypertension, hypertension with renal insufficiency: what a real evolution of knowledge these terms convey! Yet how little more than terms they are! Naming much, describing a little, they explain nothing, while the sources and paths of action of a veritable giant of mortal maladies remain buried deep as they were to the men who first recognized the disease.

I feel very diffident in talking about what has often seemed to me to be, as commonly used, a mere term or symbol. I have attended clinics, given by some of our best men, to hear the affirmation that a liberal diet of milk and eggs would increase the tuberculous patient's resistance. I have seen the man of authority impressively produce his syringe and just as impressively assure the patient that a prolonged course of tuberculin therapy would further the latter's resistance. Time and again I read that a man overcomes his tuberculosis because his resistance improves or that he fails because he has no resistance. And, hearing these statements, I have often wondered just what was going through the mind of the man who made them. Did he mean anything when he talked about resistance? Or, if he did, had he any idea of what he tried to express? Or did he merely wish to avoid mental exertion and therefore seek to explain an effect by a handy word?

If there is such a thing as resistance to tuberculosis, then it must mean that the body can protect itself in such a way that the tubercle bacillus, a parasitic invader, can gain no foothold or make but limited headway in it. We must assume further that under the influence of a specific irritant, the bacillus, the body reacts in a particular manner. As long as it reacts sufficiently to prevent or limit invasion or spread of the bacillus, just so long would we say that resistance is satisfactory. If, however, it fails to do so then resistance is lowered or absent.

The entire relation of the tubercle bacillus with the animal organism is one of reaction. *Vivre c'est réagir:* to live is to react; and from conception to final dissolution man's vital history is an unceasing period of countless myriads of reactions that go on simultaneously or unfold themselves in sequence. We must look upon every reaction to a potentially harmful stimulus or irritation as an effort at adaptation and protection. The body reacts to the rays of the sun in a certain definite manner and thus protects itself against them. It reacts to the introduction of pork or morphine in wholly different ways and thus adapts itself to them. It reacts to the implantation of the tubercle bacillus in a very particular manner, and meets the germ with the formation of a special type of cellular accumulation which we call *tubercle.*

These are trite though fundamental concepts of biology. In thinking of any tissue or organic attribute like resistance we dare not forget them, and it is likely that I shall recur to them again and again. *To live is to react.* And, if the stimulus or irritant be one that is noxious to tissue then to live is to resist. Whether resistance to a given irritant at any time is adequate is another matter, yet it is certainly true that if we are to live we must resist. Therefore, in addition to the necessary properties of assimilation, motion and reproduction, as they are generally given for protoplasm, I would add a fourth attribute, that of resistance. I am aware that this fourth attribute may be partly contingent

on the other three, but it is conceivable that in highly organized animals resistance goes on independently of them.

We assume, therefore, that there is a resistance to the tubercle bacillus; but in thus stating the proposition we have got little beyond giving a name to the known fact that tissues react to tubercle bacilli. We have not explained or illuminated a single thing. It is my purpose to inquire into the nature of this resistance, to attempt to discover how it acts and what are its effects. I trust that you will be tolerant while I lead you into regions, which, I know only too well, are strewn with obstacles and beset with pitfalls.

Let us first look into what happens when tubercle bacilli are taken into the body for the first time. In nearly all instances they enter by the mouth or nose. After excursions of varying length they pause. They may be caught in the vibrissae of the nose, or on the moist surfaces of the tortuous nasal passages, or in the mucus of the nasopharynx; and be almost immediately blown out or spat out with the nasopharyngeal secretion. Here, at the very beginning, we meet with a protective mechanism at the body's command.

But some germs, perhaps, get further. They penetrate the mucous membrane of the tonsil or pass to lymph nodes of the neck. They are now no longer *on* an epithelial surface where they cannot produce an effect: they are *in* tissue. What hap-

pens now? The tissue reacts. Fixed tissue cells begin to show unrest and agitation. There is a new and unwonted activity in cells of the connective tissue type, in endothelium lining the lymph channels and spaces. Their nuclei swell, chromatin rearranges itself and heaps up in a bizarre manner, the cells themselves enlarge, and in a short time we find that they are dividing, multiplying and piling up into collections which surround and englobe the offending parasites. Now, too, cells begin to slip in from the circulation. Leucocytes accumulate in this new, round, globoid speck of matter; and a tubercle comes to view. A few more days go by; and meanwhile we study the life cycle of this tubercle from time to time. What do we find? We notice developing under our eyes a bloodless growth or tissue formation, which englobes and encysts the parasitic invaders and thus shuts them off from the rest of the body. The bacilli are held within a globular, bloodless wall,—a wall, as it happens, of thickness and density which vary to a degree. As long as the wall is competent; as long as it holds; as long as interchange of body fluid between the interior and exterior of the tubercle is at a minimum; as long as the fibrous wall of the tubercle prevents the carrying out of bacilli from within or a flooding of body fluids from without, with a consequent softening of the tubercle, just so long will the body have the germs in this initial tubercle under control.

Fortunately, for most of us, this is the extent of our more intimate and involuntary association with tubercle bacilli. We become infected but remain free from clinical disease: we acquire tubercle but not tuberculosis. And, once having tubercle, it may be that, with never a symptom of specific illness, we will go through a long life without thoroughly eradicating the tubercle bacilli from our bodies.

Practically every one of us receives at least one infection. No doubt, infection of every degree takes place, from infection with one or several bacilli to that with huge numbers. Presumably many of the slighter infections die out completely: presumably too—for the opportunities for infection are here—their possessors again often undergo infection. There is a growing body of evidence to show that much tubercle may heal, and disappear without leaving a trace. There is also case after case to prove that much tubercle persists, either perfectly quiescent throughout life and under conditions of normal living, or for years and years, when active tubercle may develop from it. We cannot speak with scientific fulness and accuracy, but our present knowledge would make it appear that at any time most of us harbor tubercle bacilli, either those of a first infection or a reinfection, and that in a large number of us the bacilli of a first infection are never entirely wiped out, yet never bring about illness.

Why then, if all become infected, do so few of us fall ill? Where does resistance begin, what does it

consist of and how far does it go? For surely there must be some resistance: otherwise, the bacilli would multiply and spread through us like wildfire. Under the very special premises that I have outlined, is the resistance one to initial infection or implantation, or is it merely to subsequent extension and invasion? Has any man or animal a native resistance to first infection by a type of tubercle bacillus to which his kind is susceptible?

We know that several infectious diseases do not decimate civilized communities in the way in which they cut down primitive peoples. If introduced among the Esquimaux and South Sea Islanders, measles and tuberculosis are real plagues, but to-day they occur as relatively benign diseases among peoples who have a long history of community life behind them and among whom they have existed for several centuries. For this reason we postulate and teach that some groups have developed a racial immunity to tuberculosis and measles. This may be true to a certain extent; but this racial immunity is not an over-resistance to infection as such. If exposed, practically every child on earth still develops measles and practically every human being responds with tubercle. In other words, all become infected; and we cannot assume that there is any native resistance to implantation of the micro-organism.

Again, if a person is not tainted with tubercle we cannot by any known method demonstrate that he harbors substances that may be antagonistic to the

tubercle bacillus: no matter what his stock, we cannot put in evidence that he possesses an "immune substance" which a member of another race may lack. If we treat an animal by certain procedures we may find several bodies like agglutinins, aggressins, precipitins and opsonins, in its blood; yet, unless by infection we give the animal anatomic tubercle, it will not be more resistant to a given infection than any other normal and noninfected animal of the same species that has not been thus treated. Because of these facts we must assume that man and animals have no native resistance to infection by tubercle bacilli in the sense that born in them is some substance or substances that specifically destroy or neutralize tubercle bacilli that gain entrance to the body.

But, let us now examine more positive phases of resistance; and, first, what I choose to call the mechanical element in resistance to tuberculosis, an element which comes into play after the act of infection has been accomplished and its issue remains to the future.

I have often wondered why pathologists have not paid more attention to the architecture of the tubercle, as a formation designed by its very structure to resist further invasion by the bacillus. To me the most impressive feature of a tubercle is the fact that here we have a wall built around a foreign body, that the wall is formed around the foreign body to encyst it, shut it off and render it innocuous to the infected host, and that as long as the wall

holds the germs cannot get out and spread throughout the body of the host. For how does resistance manifest itself to us? Through whether infection remains confined, does it not? A spreading infection arouses in us ideas of nonresistance or a failing of resistance: a well limited one suggests that resistance of host is good. After all, tuberculosis takes on gravity as it extends its boundaries and spreads; so patent is this to us that, without thinking, we call an infection which remains limited a well-resisted one.

As long, then, as the wall holds the germs cannot get out and spread throughout the body of the host: this is resistance. And a necessary condition to the competence of the investing wall is fibrosis and a minimum of circulatory give and take between the interior of the tubercle and the tissue that surrounds it: this is *a* mechanism of resistance.

We can go even further. We can affirm that, by and large, it is the constitutional symptoms that make the clinical disease, *tuberculosis*, and that to produce symptoms of disease the tubercle must give up something in itself to the body and that the latter must absorb this material. The body can absorb something from the tubercle only if there is again a sufficient circulatory give and take between it and the tubercle, and this circulatory exchange will be directly proportionate to the degree of fibrosis or sclerosis of the investing wall.

Thus, resistance to further spread of bacilli and freedom from symptoms are to be understood not

in terms of the body producing some fighting units which go out to battle with the germs or to neutralize their poisons. They are to be understood as being the results of a mechanical barrier which the body interposes between itself and the parasites.

Suppose a man has such a tubercle in his lung and lying close to a blood vessel. It has never made itself manifest. The man has always been in perfect health. In perfect health he runs a hard race or plays a fast tennis game. Like a bolt from the sky a pulmonary haemorrhage strikes him down, and immediately he falls ill. Another man leaves home in the morning feeling well. Suppose that for years he has had a slow and sluggishly progressive tuberculous process in a bronchial lymph node, yet has never had a symptom from it. Suppose further that while he is at his desk the last tenuous sheath between this focus of caseation and the lumen of his bronchus is broken through, perhaps because of coughing or sudden muscular effort. And suppose that the contents of this focus are discharged into his bronchus and scattered broadcast. Such a man comes home in the evening sick, with beginning tuberculous pneumonia.

Suppose now that in a third man a small lymph node lay close to his thoracic duct and that firmly shut within its capsule there smouldered tubercle for years. But the time comes when the tubercle ulcerates into the thoracic duct, and from full health the man is precipitated into generalized miliary tuberculosis.

What shall we say about such patients? Shall we say that they developed acute tuberculosis because their resistance gave way? Yes, we may say so. But what did their resistance consist of? In these cases resistance surely meant that foci of infection and potential clinical disease were isolated and confined by barriers of tissue, and that when the barrier went resistance went.

Let us take another instance. Here is a tubercle in the lung, with bacilli well shut in and wall thoroughly competent under ordinary conditions and its possessor a healthy man. He develops a common cold or bronchitis and soon afterward presents symptoms of pulmonary tuberculosis. In terms of resistance how shall we view the onset of his tuberculosis? I have often heard just such cases explained in terms something like this: that the acute respiratory disease lowered the man's resistance and left him in a run-down condition, and that the cells of his body therefore lay more open to attack by the tubercle bacillus. We need not pay detailed attention to the lack of precise reasoning in such an explanation. But I should like to put forward one which seems much more plausible and square, I believe, more with physiological facts. Is it not more likely that during the man's "cold" or bronchitis there was a certain amount of congestion of the affected tissues, that this congestion extended to the neighborhood of the tubercle and that it thus established new or better channels of communication and circulation between the tubercle

and surrounding tissue, penetrating or opening the capsule and thus allowing an alteration of the anatomic character of the tubercle, or an increased absorption of focal substances, or a fresh dissemination of interned bacilli? If hard exercise will produce the circulatory conditions favorable to the breaking through of old tubercle and thus cause unlooked-for haemorrhage, why will not congestion exert a more or less similar action and bring about the same result? Here again resistance is a matter of simple mechanics: *the patient is as resistant as the shell of his tubercle.*

Hard physical exercise, sudden and intense muscular exertion, emotional stress, coughing, a common cold or other acute respiratory infection, childbirth, tuberculin in overdose, alcohol, all can produce the same circulatory effect in the neighborhood of tubercle and, theoretically at least, can bring about the same result, a better exchange between tubercle and host, with a recrudescence or enhancement of symptoms, or a mobilization of bacilli, or both. This may be momentary, it may be prolonged, it may be occasional, or it may be repeated. If the congestion or inflammatory stimulation is not overdone, proliferation and repair will set in and good may result. If it is too intense, dissemination and progression of disease may ensue. But there is no doubt that what we have been accustomed to call resistance is more or less bound up with the mechanics of the circulation around tubercle and the structure of tubercle itself. At any time every

tubercle has its maximum of stress which it can withstand: physiological activity in the neighborhood, that is, an environmental factor, supplies the stress: and whether activity or extension of infection will occur or not is always a matter of balance between the competence of the resistance against the environmental stress that may be applied.

The body responds to exercise in a definite way: the pulse rate and blood pressure rise, and respiration increases in rate and amplitude. It is not difficult to imagine how the lungs are affected under these circumstances and what might happen to old encysted tubercle, given the proper quantitative factors. We recognize this fact in treatment, particularly when we warn patients to suppress cough as much as possible: in the words of Lawrason Brown, "excessive cough is the worst form of overexercise and favors a quick deterioration of the bodily resistance." By rest we aim to put the lungs in as complete circulatory inactivity, relatively speaking, as possible, and we do raise the patient's resistance thereby. But we do this in a mechanical way by striving to avoid any manoeuvre which will enhance the activity of the lung and the tissue around the tubercle.

I have no doubt that appearances which often pass for features of resistance, or a lack of resistance, are the result of purely accidental factors. Consider those which again and again must modify the course that tuberculous infection and disease

are going to take. In our struggle to attain definite concepts and generalizations of causal relations in medicine, I sometimes think that we are all too prone to forget or disregard the large part that accident plays in the development and termination of a pathological process. One man may have vegetations on his heart valves, and these may be frequently shed off and carried to skeletal muscles: in this case no harm may result, and the event passes unnoticed. But another man with an identical cardiac condition may have the first particle which breaks loose swept into his coronary artery: and he drops dead. In a similar way accidents undoubtedly determine the course of tuberculosis. What is the leading feature of progressive tuberculosis? What makes tuberculosis progressive? It is the succession of eruptions of new tubercles which spring from the seeds of bacilli transported to new soil, now near, now remote from parent tubercles. What determines where first infection shall settle down,—the exact point where it will reside? What marks out the abiding place of daughter bacilli that are carried from older foci? No doubt, one decisive factor is the activity of the host at the particular time when infection or metastasis is taking place. His activity will be reflected in the functional activity of his organs and tissues, which respond always quickly and delicately to the variable demands made upon the several parts of the body. And what a man may be doing during the moments that infection or extension of

infection is going on is surely fortuitous. There are accidents of time and there are accidents of place.

For a moment I may touch upon the latter first. It surely makes a great deal of difference whether a first infection (or a later one) in the lungs develops near the pleura or at the root or next to a large blood vessel or at the apex. The brain is not the only organ of the body that has its silent and its eloquent areas. The lungs have theirs too: and both the immediate and later effects of identical tubercles,—identical structurally and in rate of development,—will, if the tubercles are placed differently, be not so much a matter of resistance as of location. The original localization followed no laws of resistance: it was no doubt the cumulative result of several accidental circumstances—of size of infecting clump, and driving power of the circulation of propelling lymph or blood, and calibre of channel of transport, and amplitude of respiration, and a dozen other variable moments. And a similar train of accidental forces will attend the entire life history of the infection, as it remains fixed or reaches out from place to place. To say that a man, who had a caseous lymph node erupt into the thoracic duct, went to his death with generalized miliary tuberculosis because he lacked resistance to tuberculosis, or that another man, whose cheesy neck node breaks through the skin, remains in comparative health because of his good resistance to tuberculosis, would be of a piece as to affirm that a man who fell dead lacked resistance to coronary embolism.

The first man, above cited, dies of tuberculosis; the second suffers little. Here are two dramatically opposite effects of what can easily be identical fundamental causes, *so far as the nature of the infection and the nature of the host are concerned.* The tubercles in retroperitoneal lymph nodes and in neck nodes were exactly alike in age, in rate of development, in structure, in content and virulence of bacilli, in tissue which harbored them. Wherein lay the difference of resistance? In the accident of a difference of location. And we may be sure that the same factors of accident are continually at work in the body; but as a rule beyond our observation, and deluding our senses with semblances of resistance and susceptibility—that is, if we still lisp *resistance* every time a sufferer is doing well and *lack of resistance* whenever he is failing.

And now the accidents of time. A great deal may depend on just when a patient contracts an intercurrent infection, such as acute bronchitis, or undergoes unusual strain. The same episode in his life may produce very different results. It may take place when concealed tubercle is thoroughly sclerotic and therefore proof against the changed anatomic and physiological processes going on in its neighborhood. Or it may occur at a time when the investing wall of tubercle has just the proper structure to establish fresh and easy communications with the surrounding tissues under the right conditions.

Perhaps this is why infants and young children, if compared with adults, withstand infections rel-

atively poorly so far as the effect of these on quiescent and unsuspected tubercle is concerned. Their tubercle is of comparatively recent origin and in transitional stages of development, and is much more imperfectly fibrosed or healed and is thus more open to outside forces. As they grow older, this healing process has advanced further and further, and encapsulation of bacilli is better established. We are familiar with the result: for we say that in regard to tuberculosis five to fifteen years is the golden age of man's span. Infection tests disclose roughly that about one-half of us city dwellers are infected by age five or six, and three-fourths by fifteen years. This means that two-thirds of the infected strike contact with tubercle bacilli during the first six years of life; and that, for most children in mid-childhood and later, whatever infection persists is relatively old.

After we pass puberty we enter a period of from fifteen to twenty years when life's stresses are at their maximum and our reactions to them at the same time more intense and vigorous. In many cases this increased mental and physical strain produces local effects which are more upsetting than even healed tubercle will bear. I say "healed" with some mental reservation. Perfect healing, as we have seen, can and does take place. But healing is not infrequently more apparent than real; for I would have you recall that living tubercle bacilli have been found in the chalky deposits of tuberculous foci that had healed with calcification. It is

for these reasons that I am very fond of telling our students that the development of tuberculous disease from old benign tubercle depends largely on whether the patient gets measles or a cold, or rows a race, or becomes pregnant, or goes into bankruptcy at the wrong time.

We have thus far discussed the protective reaction by which the tissues seek to hem in and wall off the first tubercle bacilli that enter the body and exert an effect upon it. We have also considered local conditions through which the body resists the development of tuberculosis. We have looked upon tubercle as a growth or formation, the periphery of which acts as a barrier to the egress of bacilli, yet is subject to all the physiological disturbance that goes on around it. We have seen how the permanence of benign tubercle or the conversion of this into tuberculosis with symptoms will depend largely on the mechanical interaction and balance of these opposing forces. We may anticipate; and forecast that upon the latter will play many factors of heredity, environment and acquired characteristics, such as new methods and habits of bodily reaction specifically created by the infection. We may now extend our analysis to an inquiry into those conditions which bring into being the patient who presents himself to us with active tuberculosis.

A person with tuberculosis consults a physician because he has symptoms due to his infection, be these ever so slight or ill-defined. If he noticed

nothing unusual, uncomfortable or wrong, he would not seek medical light and counsel. *Symptoms, and symptoms alone, betray active tuberculosis.*

Few persons, except very young infants, pass at once and uninterruptedly from initial tuberculous infection to symptoms. Between the two incidents there is an interval of weeks perhaps in a few, or months or years in most. All our experience would teach us that the ordinary course of the infection, even in those who become ill, is marked by longer or shorter periods of development and subsidence, and of extension and retreat of morbid anatomic change, before first symptoms make themselves felt. At his very first visit to the physician, the usual tuberculosis patient has never, I believe, only a single focus which represents the exact spot where first infection took hold. In the simplest and most elementary cases there are undoubtedly several foci. In some these may all be comprehended within a very small space, yet they represent extensions from some older area or areas, and there will always be infection of adjacent lymph nodes, whether this is obvious or not.

A process like this takes time to evolve. It comes into being haltingly, and by fits and starts, and, until symptoms at last come forward, insensibly, and unknown to the possessor. As one reads the general run of papers on tuberculosis, one gets the impression that a good deal of hair-splitting has attended our efforts to arrive at a concept and definition of activity. Attempts to limit the idea of activity to

those cases which exhibit symptoms, either spontaneously or after certain tests of function, provoke the rejoinder that there is or can be an activity without symptoms—a state that goes under the designation of *pathological activity*.

This is all very true; but what of it? As a matter of fact, every soul alive who responds to infection tests must have had some pathological activity. Infection tests are indices of the presence of tubercle, and the formation of even microscopic tubercle represents the stirring at some time or other of some pathological activity. The proliferation of a dozen cells in response to a single tubercle bacillus is pathological activity. No tubercle ever came to light except through pathological activity. Presumably, no man who has taken in bacilli which tarried for a time has ever escaped pathological activity of his infection.

But 80 or 90 per cent of us recipients and carriers of infection never experience a symptom of it. Pathological activity, therefore, takes on significance only as it brings on that state which will be expressed symptomatically. Attention to pathological activity can no doubt serve its purpose; for instance, *in the patient with established clinical tuberculosis*, when we wish to anticipate whether symptoms are likely to improve or grow worse. But one will be hard put to it to use with any degree of accuracy standards of pathological activity to detect or forecast or prevent the onset of clinical tuberculosis. *Phthisiogenesis in practice begins when symptoms begin.*

The man with pulmonary tuberculosis becomes a patient not after a lobule or a lobe or a whole lung becomes a tuberculous structure, but as soon as he displays symptoms that are undoubtedly those of tuberculosis, even though morbid change is so slight or so concealed as to be beyond our observation.

There is the man with haemoptysis who reveals nothing to the stethoscope or the Coolidge tube: he has active tuberculosis. There is the man who has the work of twenty years of pathological activity moulded within his chest, a storehouse of abnormal signs and shadows: yet, never ill or disabled, his disease has never been active.

Active tuberculosis, then, is tuberculous infection with symptoms. But why symptoms? Under what circumstances, symptoms? If we answer these questions we likewise throw some light on the mystery of why some with infection develop active tuberculosis while in most the infection remains quiescent. And if, as is often maintained, "resistance" is the force which keeps infection inactive, we may also contribute something to an understanding of resistance.

For thoroughly good and sound reasons the symptoms of tuberculosis have long been classified as of two types, which differ in mode of origin and in part affected. We recognize some as local symptoms and others as constitutional symptoms. We find that the former are manifestations of impaired function or tissue damage, of structures in which tubercle is present, and that this impair-

ment or damage results largely from physical forces directly applied by the tubercle and set in play by it. On the other hand the constitutional symptoms affect the body as a whole or parts of it remote from the seat of disease, and are plainly the effects of some noxious substances which are given out by the tubercle and transported to centres which regulate the more general body functions.

Tissues may be damaged by the local effects of tubercle in a way that precludes complete restitution to normal. Local symptoms may therefore persist after tuberculous infection has died out or after anatomic repair is concluded. They may, therefore, continue after arrest of clinical activity. But the possibility of inactivity cannot be entertained as long as constitutional symptoms are manifest or can be induced. Constitutional symptoms become therefore our best indicator and guide of activity, and it is these which may illumine the indefinite and shadowy line between the actual and potential patient.

Why has the actual patient constitutional symptoms? Because he is absorbing something from his foci of disease. Why does he absorb something? Because there is a sufficient circulatory (blood and lymphatic) give and take between his foci and the surrounding tissue. Why this circulatory give and take? Because the walls, the envelopes, the investments of these foci are not competent to block off the interior of the tubercles against particular outside forces that may be brought to bear upon them.

If, in course of time, these walls become more and more fibrous and more impervious, the severity of the patient's symptoms will surely diminish. Passage of focal substances will be much less through a dense and thick envelope than through a thin or filmy one, and an enhanced circulation and lymph content around tubercle will bring about those physical conditions which promote this transit. The rate and amount of absorption of focal material, therefore intoxication, therefore constitutional symptoms, will always be governed by these two factors.

This fact is so obvious that I consider it hardly necessary to enlarge upon it. Designedly or otherwise, we put into practice this principle in every recognized method of treating our patients.

When we induce artificial pneumothorax, we exert the most direct effect upon the process in the lungs. Just what do we aim to do? To put the lung at rest, of course. Yes, but what happens then? The excursions of the lung cease, its circulation becomes relatively quiet, less lymph bathes the tissues, absorption from foci of disease goes on at a much lower level or stops altogether, constitutional symptoms improve and disappear, and with a lessening of hyperaemia around the morbid process peripheral fibrosis goes on better.

Or we put the symptomatic patient at bodily rest. With the slowing down of circulation and respiration, symptoms may abate—often with astonishing rapidity. If now we allow our patient to exercise, symptoms recur—perhaps immediately. This sub-

sidence of or relief from symptoms cannot be due to any neutralizing agents which the body elaborates, for we cannot imagine that such a prompt response to rest or exercise would occur under these circumstances. Rest and exercise exert an immediate effect on respiration and circulation and these in turn set the pace for focal absorption. It is not uncommon for patients who suffered markedly from the constitutional symptoms of absorption while they had incipient tuberculosis to inform you that they feel better after bacilli appear in their sputum. Bacilli in the sputum usually means that the pulmonary process has ulcerated. Here by ulceration Nature has applied the prime surgical procedure of more or less thorough evacuation of disease with a consequent amelioration of constitutional symptoms.

In another instance it may happen that we give an entirely asymptomatic patient an overdose of tuberculin. Malaise, fever, rapid pulse, distaste for food, all the well known constitutional symptoms of tuberculosis, promptly appear. Tuberculin is not a bodily poison: it will not make ill a man without tubercle. What happens then in the man with tubercle? Undoubtedly something like this: Tuberculin exerts a direct inflammatory effect on the tissues of animal bodies that harbor tubercle. This action is particularly marked on those tissues which are immediately adjacent to and in contact with tubercle. They inflame; and there results the well known focal tuberculin reaction, a phenomenon that is marked by hyeraemia, congestion and inflamma-

tion which, beginning in nearby nontuberculous tissue, rapidly comes to involve the tubercle. After giving tuberculin to a rabbit with corneal tubercle it is instructive and impressive to watch healthy eyelids become red, and then fine blood vessels come into view and push their way across the cornea to the focus of disease, and the entire eye soon involved in acute inflammation. Here, then, is the same enhanced circulation, which we have been discussing, affecting the envelope of tubercle in a way that tends to make it more open, and promoting the insweep of material from focus to the general circulation.

Marcus Paterson gets the same immediate result without recourse to a specific agent like tuberculin. He simply puts his patients to work until they get what he terms an "auto-inoculation." And how do we recognize this auto-inoculation? By the same familiar constitutional symptoms of active tuberculosis or of the general tuberculin reaction which is really an evanescent episode of active tuberculosis. The investment of every tuberculous structure has its own limit of resistance to stress—to amount, pressure and velocity of lymph and blood flow and to rate and amplitude of respiratory excursion which, of course, influence the former. As soon as the labor prescribed by Paterson brings into play the proper amount of stress, the particular patient will take over to his body focal material enough to bring on constitutional symptoms.

The point is that the presence or absence of symptoms is to a large extent contingent on focal mechanics. I think that we can say with perfect assurance that increasing fibrosis means a gradual release from symptoms, while increasing degeneration and necrosis—softening, as we term it—without coincident and sufficient peripheral fibrosis mean added severity of symptoms. The man who has extensive anatomic tubercle with comparative freedom from symptoms has his tuberculous process well sclerosed and hemmed in. The man who has marked constitutional disturbance with but slight anatomic change has very slight or imperfect focal investment. Whether inactivity passes over to manifest disease is frequently determined, not by any lack or failure of a hypothetical inherent quality of tissue or bodily resistance, but by experiences which infected persons are called upon to undergo, experiences which set up functional disturbance sufficient to bring about that amount of focal absorption which is sufficient to produce symptoms. Granted that the patient, that most of us, possess an indefinable specific resistance, this remains the same while we lapse from latency to activity under the spur of an unusual environment. Resistance, inborn or inbred in tissues, is not wiped out in the minute that it takes to run a quarter-mile or the fraction of a second that compasses the impact of a club with the chest, yet this interval will change a healthy person into one sick with tuberculosis. I would not maintain that this mechanical element is

all that there is to resistance to symptoms. In fact, I plan to discuss other components in the course of this essay. But the mechanical side looms large in any check which the body offers to the manifestations of the disease.

And, as far as any extension of anatomic change is concerned, we can neglect all other factors and assert almost dogmatically that, as long as fibrosis is the predominant element in any particular case, just so long are fresh eruptions of tubercles much less likely to occur than if degeneration and caseation had gained the upper hand. What gives us our conception of progressive tuberculosis? It is extension and spreading of the infection. While clinical (or latent) infection remains limited and well localized we are accustomed to think of its possessor as resistant; just as we speak of a failure of resistance when we observe infection enlarging its boundaries or being repeated in daughter foci from place to place. Again, we may admit the actuality of a native or acquired habit of bodily constitution which we, in various degrees of vagueness, conceive of as joining in effective combat with the germs of disease, and which we may call resistance; but we would at the same time hold fast to a view of a resistance which consisted in large measure of local mechanical conditions unfavorable to first infection or later eruptions.

Besides the physical resistance which the body, through the production of peculiarly designed structures, offers to the release of symptoms and the

spread of infection, it also possesses an entire system of highly competent mechanical checks and barriers which must enter into any comprehensive concept of resistance.

Tuberculosis is essentially a lymphatic infection. Entering by digestive tract, the germs penetrate the mucous membrane of mouth, throat or intestine, and come at once within the domain of the lymphatic system. In very many instances they pass immediately into lymphoid tissue like the tonsils or the follicles of the intestine. If they are carried further into the body, always by lymphatic paths, they are soon intercepted by lymph nodes. So far as I know, the evolution of the parts and organs of the body has not proceeded capriciously. I cannot imagine that the lymphoid tissue, nodes, follicles, etc., of the body owe their particular distribution and quantity, which vary for the several animal species, to the requirements of ornament, symmetry or the prime animal functions of "getting and begetting." As a matter of fact, they are always situated in greatest abundance near those places where there are the greatest numbers of foreign bodies (bacteria) or they communicate directly with these. The neck is an example of this circumstance, and the enormous increase of lymphoid tissue which becomes manifest as we proceed from the highly motile and bacteria-poor small intestine to the relatively sluggish and bacteria-rich large intestine is a striking instance. Wherever the normal processes of life make for most irritation of superficial tissues through

foreign bodies, as well as promote the entrance of these particles into the depths of the tissues, there you are bound to find lymphoid tissue relatively plentiful. We cannot view the lymphoid tissue otherwise than as taking an important part in blocking the passage of bacteria to more vital organs.

Bacilli which gain any part of the respiratory tract in the nontuberculous young are for the most part similarly carried to lymphoid tissue,—to the deep nodes of the neck or those at the roots of the lungs. Those, again, which come to the lungs by the blood from foci elsewhere in the body, tend in early life to be carried out of the transporting blood vessels into the lymphatic network of the lungs and proceed by way of this to the root nodes.

It happens, therefore, that the ordinary early tuberculous infections of life, which almost everyone to-day acquires, are first localized in lymph nodes, usually the submaxillaries and deep cervicals, the tracheobronchials and mesenterics. It happens also that, when disease manifests itself in early life, it does so most frequently in these nodes or, in a large proportion of cases of extralymphatic disease, its origin can be traced to these nodes.

What is significant is that in the great majority of infections—fully 90 per cent—the lymph nodes are competent in restraining the infection and keeping it quiescent. In experimental work I have long been impressed by the great resistance which they offer to the spread of infection, and particularly

to the development of progressive and florid disease within themselves. In guinea pigs, unless the nodes are receiving large and continuous doses of virulent bacilli from more superficial foci which they drain, they will keep under control astonishing amounts of infection without becoming markedly diseased. The average picture is tumefaction, with caseation which is well balanced by sclerosis; to an extent, indeed, that, if we consider all nodes in the body, sclerosis usually gains the upper hand and comparative healing is the result. When infection seizes upon those smaller collections of lymphatic tissue which reside normally *within* organs and which are not true nodes, as in the spleen, the result is usually different; for it is in these places that we are accustomed to find infection developing and progressing. Yet, as has just been mentioned, these are not true nodes: their structure is quite different as regards tortuosity of lymphatic vessels and spaces within them and they usually exist in peculiarly intimate relationship with blood vessels.

Now, lymph nodes and lymphoid collections are intercalated at innumerable places along the paths of that wonderfully luxuriant and intricate meshwork of lymphatics which courses everywhere in the body. They undoubtedly intercept many bacteria in their transit from the surfaces of the body to the interior and thus preserve important organs from massive and telling infection and contribute to general resistance to tuberculosis. They surely do this in a mechanical way by holding up bacilli: a "filtering"

process is the popular conception, but quite likely this is not wholly accurate.

Whether they also act by destroying tubercle bacilli through the agency of some constituent peculiar to themselves, the lymphocyte for instance, is among the undetermined problems of resistance to tuberculosis. For thirty years and more there has been published an enormous amount of work designed to prove that lymphocytes are bactericidal for tubercle bacilli. This may be true. But whether lymphocytic activity is an important element of resistance to tuberculosis must surely be considered as open to argument to-day. We meet with undoubtedly increased resistance to the infection again and again, under circumstances that fail to disclose any association with lymphocytes. The fact, known for three decades, that tubercle bacilli may persist in small numbers in lymph nodes for a long time speaks against a specific ultra-antagonism of lymphocytes to them. The tendency of infection to develop more in lymphoid collections which are not true nodes than in real lymph nodes suggests strongly that the structure of the latter is a more potent restraining influence than the properties of any cells peculiar to it.

Whatever be the agent at work—and I consider a mechanical action as surely playing a part here—the fact remains that the lymph nodes in general put limits to tuberculosis. The more I observe infection and disease in human beings and in animals of experiment, the more I am impressed with the

function of these small organs as instruments of high resistance to the unchecked spread of tuberculosis. A sound and competent lymphatic system is a strong defense. Unobstructed lymphatic paths, permitting free and easy passage to the nodes, will allow focalization in the nodes themselves where the bacilli are comparatively harmless. Blocked channels promote the settling down of germs in tissues, the infection of which may be of graver concern. Nodes placed between the portal of entry and an organ spare the central organ. Open lymphatic channels with normal lymph flow in an organ tend to carry bacteria away from a part and thus spare a peripheral organ.

Our argument thus far has been concerned with establishing the position that nonspecific factors can play a decisive part in contributing to a result which has all the appearances of being due to a resistance or a susceptibility to infection and disease. That is to say, inactivity puts on a face of an infection being resisted well, and activity the reverse. What does really determine activity or latency at times are purely accidental factors of location of infection and time of occurrence of those stresses capable of exciting foci of tubercle to renewed vigor. At the same time, in every instance there is always another resistance which stands between the body and the activities of the parasite. We have designated this as a mechanical resistance, one that comes about through the interposition of two important barriers

between germ and host. These are the systems of lymph nodes, a function of which is to intercept and restrain foreign particles, and the peripheral part or investing envelope of every tuberculous process. This mechanical resistance is more or less competent and sufficient, according as a part of the lymphatic system concerned is functioning more or less normally, as peripheral fibrosis of tubercle keeps ahead of or behind central degeneration and necrosis.

All this, of course, has been hardly anything more enlightening than a sharper delineation of concepts. It has made little progress to the root of the matter. Although we may say that good resistance is the accompaniment of a sound and competent lymphatic system and of tubercle that scleroses rather than "softens" and breaks down, before we can venture to understand why resistance is high or low we must explain why lymphatic systems differ and why some tubercles run to scar tissue rather than to caseation.

A partial explanation is to be found in much that we have already said. The integrity of the lymphatic system and of tubercle is frequently influenced and its character altered by antecedent experiences (environment) of the person. This is so plain that it need not be gone into further.

But there is undoubtedly a good deal more than this at work. The manner in which tissues react determines in no small measure fibrosis and caseation, degeneration and repair,—that is, resistance.

Underlying this there is always the presumption that different bodily constitutions vary in their kinds and capacities of reaction, either natively through inheritance or through acquired attributes. There are also marked differences of congenital lymphatic constitution and behavior: these have always been so noticeable that we have long recognized the more prominent manifestations as deserving of special classification and have tried to bring under the "lymphatic diathesis" everything from unusual tendency to adenoid growths to "lymphatism" and "status lymphaticus." The numerous and multiform congenital aberrations of the lymphatic system and their significance in relation to infections receive attention in every textbook on medicine. They will therefore hardly repay discussion here, except that I would point out that, whatever be their real nature and whether they represent primary and essential abnormalities by inheritance or merely reflect more deep-seated changes of the same nature, they are striking examples of an apparent association of congenital traits and a resistance to infections that is below par. It will no doubt be more profitable to confine the rest of our discussion to an examination of the probable factors that influence or determine the reaction to irritation in general and to the tubercle bacillus in particular.

The ability to form defensive tubercle is a native or basic attribute of tissues. It is at bottom the power to react to a certain type of irritation by the multiplication (*proliferation*) and proper arrange-

ment of cells. We would assume that the capacity to react vigorously to a given irritant in this way would make for better protection than a feeble reacting power. In the case of infections, over-reaction makes for better defense than under-reaction.

Every observing man must be impressed by the diversity of reacting power exhibited by different people to the same irritant. A very familiar example is the varied response to sunlight, through sunburn, freckles and tanning. Some men, when wounded, will react with a great overgrowth of scar tissue (keloid); others, after injury that does not seem different in kind or degree, will exhibit only a flat and scarcely noticeable scar. Whether one tans or is sunburned or produces keloid is surely dependent on a native, inherited variation of ability to react to irritation. In the case of these particular irritants, individual, family and racial variations have long been recognized.

It may very well be that many variations of basic reacting capacity come into play in all the contacts that are established between us and many irritants. We know that the metabolic fault that gives rise to gout is inherited. People do not get gout only because they eat and drink certain things that will give them gout. They suffer from the disease because the tendency to gout was born in them: others who were not born with this tendency may eat and drink gout-precipitating foods with impunity. The tendency is quite likely a constitutional aberra-

tion or "vice." Many gouty people belong to a distinctly marked physical type: they are short-necked and thick-set and have florid complexions and reddish hair—all inherited characteristics which frequently go hand in hand with the gouty predisposition. And, in this connection, it may be mentioned that the gouty have always been looked upon as being peculiarly resistant to tuberculosis.

Diabetes, another disease of metabolism, as yet very imperfectly understood, also appears in certain families to such an extent and occurs with such frequency in the Jewish race that an inherited basis for it is highly probable. Diabetics are unusually prone to tuberculosis.

Maud Slye's experimental work is extremely significant in the matter which we are discussing. She works with two large series of mice. The one consists of animals that have had cancer bred into them; the other, of those which she is continually fortifying with a cancer heredity by mating their progenitors with members of known cancerous stock. She finds that animals of the cancerous strains react very differently to irritation than do those of non-cancerous stocks. If injured, many of the first type develop cancer at the site of the wound, while none of noncancerous inheritance ever reacts with cancer under the same conditions. Many of the latter, however, become ill with the ordinary infections of cage life and die. Among the members of cancerous strains, infections are very unusual and, if they occur, are resisted well. She would therefore generalize

about as follows: Cancer is the result of a congenital tendency to overreaction to irritation. Animals with this tendency do not easily acquire infections. If they do develop them they resist them well. Infections strike down the weak. Cancer attacks the strong.

If Maud Slye's work is sound what shall we say? Shall we conclude that the same tissue tendency that is responsible for cancer also protects against infection? Shall we assume that the irritant, the parasitic microörganism, gains slight foothold or none at all because it is immediately met by an exaggerated effort on the part of the body cells to ward it off? I am here reminded of a remark which that wonderfully keen observer, Dr. Trudeau, repeatedly made—that cancer is a disease of the strong, progressive tuberculosis a disease of the weak. He undoubtedly based this opinion on his impression that so many people who developed cancer had clinical histories which were relatively free from infections during earlier life.

Granted that certain capacities of reacting to irritation are born with the person, it is also likely that the individual's native manner of reaction responds to outside influences and is modifiable by these. We shall see that this is certain when tubercle bacilli infect susceptible animals. But this modification of the way of meeting irritation—of resisting infection—no doubt also takes place under less specific conditions. I have been highly impressed by a circumstance which I have observed

several times during the course of infection experiments. If we introduce living virulent tubercle bacilli between the layers of the skin of normal guinea pigs we may study with particular accuracy the natural evolution of tubercle. The entire process comes to light and grows under our eyes. Now tubercle develops in these cases because inoculated tissues react to tubercle bacilli: there might be a flourishing of bacilli, perhaps a septicemia, in the absence of cellular reaction, but there would be no pathological anatomic process, no characteristic tissue change, no tubercle. But in several series of inoculations it has occurred that if sick, nontuberculous animals were included in the series, they did not respond to the introduction of bacilli with the formation of tubercle. They lived long enough to develop tubercle, through a period in which all the healthy members of the series, similarly inoculated, did show tubercle; yet sick, weak and thin, as they were from other disease, they remained free from visible tubercle.

Observations of this kind surely suggest that an intercurrent disease had deprived some animals of their native capacity to react to tubercle bacilli, to form tubercle. Presumably, also, their resistance to tuberculous infection was also changed by the intercurrent infection. It is surely not a wild assumption that any alteration of resistance would dwell in a changed capacity of cellular reaction such as I have described.

All in all, I think that we may assume with every assurance of justification that men do vary in response to irritation. They vary by birth, if compared with one another, and the same man may vary at different periods under the influence of external forces. This variation of response may take the form of overreaction, overgrowth or overproduction of tissue, or of predominant tendency to fibrosis, all of which may become revealed to us as increased resistance to infection.

If any foreign body that is not easily assimilable gains access to the body the tissues react in a characteristic way, that is, with the formation of tubercle. Similarly, tubercle bacilli which are more or less nonassimilable by the tissues incite the formation of tubercle. Now there are several things which will modify this type of reaction against the irritant. One is the number of infecting bacilli. Long ago Baumgarten pointed out that if tubercle bacilli were very few the earliest tissue response would be manifested by the proliferation of only one type of cell. If, following a first infection, only a few bacilli lodge at a point, then for several days the only reaction which we note is a proliferation or new growth of those cells which belong to what we designate as the fixed-tissue type. The resulting structure is a minute mass, a nodule or tubercle, which has many features of a tumor and few of the essentials of an inflammation. Such an early tubercle may be made up of cells of the fixed-tissue type alone: there may not be a leucocyte or any other

element of inflammation or exudation in it. Here we have really a new growth or tumor, comparable to what under ordinary circumstances we would call a fibroma.

If, however, the initial number of tubercle bacilli is large, the first reaction is an outpouring of polymorphonuclear leucocytes. But within a few hours the fixed-tissue cells begin to show signs of disturbance, and proliferate. The polymorphonuclear leucocytes soon disappear, and tubercle formation goes on characteristically, with a gradual inwandering of leucocytes, mostly of lymphocytic nature, which distribute themselves, in diminishing numbers from periphery to centre, throughout the mass of fixed-tissue cells now termed *epithelioid* in this location.

We see, therefore, that under ordinary conditions the body reacts *to first infection* in a variable manner, according as the irritation is more or less vigorous and intense. But the reaction is very regular and definite and, if the infecting bacilli be the first that have settled in the body, the result will always be the same in that this initial reaction will manifest itself as *focal* tubercle. The relative proportion of epithelioid cells and leucocytes in different tubercles may vary, but the response to first infection will always be focal, with tubercles very definite, isolated and discrete formations, with bacilli near the centre, and concentric layers of epithelioid cells interspersed with leucocytes forming the periphery. And as we look at them we think of the wall or barrier about which we have said so much.

These reactions go on in a perfectly orderly manner. Microscopically, they begin to be evident a few hours after inoculation, if ordinary doses of bacilli are used: macroscopically, they come into view from about the eighth to fifteenth day on. At the same time, we observe a feature of the utmost importance. This is that the animal of experiment never exhibits a single trace of illness which can be attributed to the immediate or early effects of the first infection. No matter how large the dose and no matter how inoculated, the first bacilli will never bring about any visible change in the guinea pig's or rabbit's general health. Immediately after the infection, and for days and several weeks, these animals are as lively and eat as well and have the same muscle tone as though nothing unusual had happened to them. It is only in the fourth, fifth or sixth week after inoculation that they begin to show a falling off in health.

All these constitute the more apparent features of what we may call the essential or native or inherited response of susceptible animals to tubercle bacilli—that reaction which meets a first infection. Put a little more sharply, they are (1) extreme sluggishness of reaction, (2) lack of inflammatory phenomena, (3) predominance of proliferative phenomena, with the consequent formation of discrete nodule or tubercle, and (4) total absence of intoxication or any symptoms.

But as soon as infection is established and tubercles are formed, the capacity of these animals to

react to tubercle bacilli or any of their dissociated protein constituents is changed. For instance, the series of events is quite different following reinfection.

Then—that is, after reinoculation of an already tuberculous animal—both local and constitutional changes take place with great promptness and celerity. We may perform such reinfection on the same animals to which we applied tubercle bacilli a few weeks before and which responded as we have described in the preceding paragraphs. But now we observe (1) extreme rapidity of appearance and development of tissue changes at the points where new bacilli focalize, (2) redness, swelling and even tissue death, in other words, inflammation, appearing at these points within a few hours after reinfection, (3) more vigorous and accelerated proliferation of fixed-tissue cells which, however, is abortive and soon reaches an acme beyond which it does not progress, and (4) rapid intoxication of the animal, with illness within a few hours and, often, death in less than a day.

Although a few men, as long as a half-century ago, had observed this changed habit of reaction, which tuberculous infection confers, we really remained in ignorance of it until 1906, when Pirquet announced his skin test of tuberculosis to the world. We first really learned something about it through the application, not of living tubercle bacilli, but of their derivative, *tuberculin*.

Tuberculin contains nothing virulent or alive. It has in it products of tubercle bacilli, usually in a soluble form. If an animal is without tuberculous infection it will tolerate tuberculin with the same facility as it would a mixture of glycerin and broth that is without products of tubercle bacilli but in other respects resembles tuberculin. It will remain well if large amounts of tuberculin are put beneath its skin or into its belly or a vein. It will exhibit no local response, no swelling or redness or soreness, to tuberculin applied to its skin through a scratch or with a needle into the skin. In other words, a nontuberculous animal will not react to a single application of tuberculin, either immediately or ultimately. The essential or native or inherited reaction of animals to tuberculin is nil.

Not so that of the tuberculous animal, however. Infection with tubercle bacilli endows animals with something besides tubercle. It changes their whole manner of meeting the application of tuberculin. It "trains" their tissues to react to tuberculin with inflammation and their body to react with intoxication. A minute amount of tuberculin put into the skin of a tuberculous animal will provoke redness, swelling and soreness at the point within a few hours; injected beneath the skin or into the belly or a vein, it will prostrate the animal with fever and malaise.

To sum up then: *Anatomic tubercle, consequent to the introduction of tubercle bacilli, so changes the animal body that its tissues react differently from the normal to the application of any soluble protein prod-*

ucts of tubercle bacilli or to the reintroduction (reimplantation) of living or dead bacilli.

This newly acquired attribute of tissues has been aptly denominated as *allergy* (ἄλλον + ἔργον or different action), a term coined by Pirquet. As we learn more about allergy, we are coming to realize that it plays a prominent and at times a preponderant part in all the phenomena of tuberculosis. Appreciation of its manifestations are demanding that we look at many phases of tuberculosis from new points of view. It is desirable that in this essay I restrict a discussion of allergy to an inquiry into its probable relations to resistance to tuberculosis. But even this limitation will encroach on pathological and clinical phases of the infection. And, lest I should otherwise run the risk of obscurity and incoherence, I deem a digression on the nature and characteristics of allergy necessary in this place.

1. Conditions necessary for the development and recognition of allergy: These have already been touched upon. No dissociated substances of tubercle bacilli have ever to a certainty brought about the allergic state. *Only tubercle bacilli—living or dead—have produced it.* Allergy due to dead bacilli is inconstant, feeble and transitory; that set up by living bacilli in a previously normal animal is remarkably invariable, marked and durable. In other words, *there exists no allergy without tubercle.*

The allergic state is recognized by the allergic reaction, that is, the rapid inflammatory responses

mentioned above, to the proper substance necessary to elicit it (*antigen*). The proper antigen is living or dead tubercle bacilli or any dissociated product of these which contains protein (tuberculin). Thus, *while dissociated tuberculoprotein cannot give rise to the allergic state, the true allergic reaction is apparently set in motion only by tuberculoprotein, whether dissociated or contained in intact bacilli.* Therefore, until the contrary is proved, we would class allergy among bioreactions to protein.

2. The time relations of allergy: According to the virulence and dosage of the infecting bacilli, the first manifestations of allergy are to be elicited in an animal (guinea pig) at from six to twenty-five days after first infection, that is, at about the time of the first development of tubercle. The same relations apparently hold in man (Hamburger, Hess). All experimentation indicates that it persists as long as specific tubercle remains in the body.

3. The variations and fluctuations of allergy: The capacity for allergy varies greatly in several animal species. Man is apparently the most sensitive animal: at any rate, he will react to the smallest doses of tuberculin—and presumptively, therefore, to the smallest numbers of tubercle bacilli. The sheep is highly allergic (Roemer). The guinea pig has a much lower capacity for tissue hypersensitiveness than man or the sheep. For instance, no guinea pig, however tuberculous, will react to tuberculin applied through a scratch or scarification à la Pirquet. It will, however, react very consist-

ently and vigorously to the *intracutaneous* application of the proper amount of tuberculin, an amount which is far in excess of that capable of eliciting a response in man. The rabbit is the least sensitive of all animals commonly experimented with: its skin reactions are inconstant and comparatively feeble.

Experiment shows that allergy follows quantitative and qualitative curves, that is, variations of degree and intensity, which are roughly parallel with the development and progression or retrogression of infection. Studies, published by me several years ago, pointed out very sharply that allergy in guinea pigs inoculated with virulent human bacilli began at about ten to fifteen days after infection and increased progressively with the evolution and extension of infection until the animals became moribund. It proceeded differently, however, in guinea pigs that had been inoculated with relatively avirulent human bacilli, which, while arousing the formation of tubercle, did not kill the animals. The latter were frequently tested and studied through a period of almost two years. Their allergic course was about as follows: Allergy first appeared a few days later than in the virulently infected animals; autopsy showed that tubercle also developed more slowly. With the growth and progression of tubercle, allergy increased to a marked and constant degree, but it never reached as high a point as in the virulently infected animals. After about forty days it reached a "plateau" which it

held for a long time—for months. Then, while physical examination and autopsy were revealing that tubercle was receding and was being arrested, allergy began to diminish. It continued to fall until it became very slight. In no case, however, did it disappear, that is, return to the base line or level represented by the native or original capacity of the animals to react. Autopsy with microscopic examination of tissues of these slightly reacting animals, 697 days after infection, showed only very sclerotic and very well invested tubercle in lymph nodes related to the point of inoculation.

Highly instructive was the behavior toward reinfection of these animals with falling allergy. They were given a second inoculation of living tubercle bacilli, 669 days after their first infection. This new infection promptly and markedly intensified a diminishing power to react.

We are therefore led to believe that in life, and under the influence of infection (tubercle), the allergic state is continually fluctuating, now lazily, now sharply, with the amount and pathological condition (competence of investment, opportunities for focal absorption, etc.) of tubercle. It is heightened for longer or shorter intervals by extension or metastasis of infection, or by reinfection; or it is becoming feebler as the sum total of sclerosis keeps ahead of the sum total of degeneration or fresh extension; all this, so long as the physiological activities of the animal remain fairly stabilized. Our methods for estimating these relations of quan-

tity and quality are so crude that finer variations of allergy in the human being are either impossible of detection or equivocal of interpretation. But it is not to be doubted that these fluctuations are going on continually in whoever carries tubercle.

At this place, also, I would merely refer to the well-known diminution of allergy which attends intercurrent febrile diseases, pregnancy, perhaps fatigue, etc., in tuberculous animals. It is important to remember, likewise, that during the height of a general tuberculin reaction and for a short time after it, allergy may fall to the vanishing point. It may similarly be greatly blunted during certain phases of acute tuberculosis.

4. The tissues affected by the allergic state: Allergy is best known and usually recognized through the easily obtainable inflammatory reactions of the skin and mucous membranes of persons with tubercle. But all studies made thus far would indicate that all the tissues of a tuberculous animal are allergic (Trudeau and Nichols on the lung, Léon-Kindberg on the kidney, Paterson on the pleura, Soper on the liver, etc.). Whether at a given time all the tissues are allergic to the same extent is an important question that has not yet been investigated—probably because of the very great potential source of error in any experimental technique which would approach this problem.

5. Tuberculous foci are highly allergic: While the comparative allergic capacity of the several uninvolved tissues of a tuberculous animal is a problem

awaiting investigation, there is no question about the much greater reacting quality of tuberculous foci, or, perhaps more accurately, of tissues containing tubercle, if these be compared with non-tuberculous tissues of the same animal. As is well known, foci of tubercle anywhere in the body react with acute inflammation to tuberculin put into the body at a remote place. This *focal reaction* is nothing else than an allergic reaction. The amount of tuberculin which reaches foci, under these conditions, must often be extraordinarily minute: the results are frequently intense, even violent, as may be learned from the animal of experiment. A very small amount of tuberculin, superficially and directly applied, will inflame a tuberculous ulcer (Sternberg); or, allowed to drain by skin lymphatics to a patch of lupus, may induce a violent reaction in the latter. When tuberculin is given subcutaneously and thus becomes distributed throughout the body by lymph and blood, whole organs which harbor tubercle may rapidly undergo hyperaemia, congestion or the more advanced grades of inflammation, even though their visible tubercle is slight and isolated. In general, it may be said that the competence of investment of a given tubercle will govern its capacity to react: old, sclerotic processes are much harder to throw into reaction than are young or softening ones.

6. Trauma not necessary to elicit allergy: Because the skin or mucous membrane must be punctured to bring about the reaction, it may be thought that

reaction will occur only when a tissue is wounded. But focal reactions, and the inflammations following the introduction of reinfecting bacilli by way of the blood, at points where these focalize in internal organs, teach us that reaction may take place without the application of trauma; unless, indeed, in the latter event the focalization (embolization) of bacilli highly resistant to outside influences may be conceived as a traumatizing act.

7. Variations of intensity of the allergic reaction: The reaction may run the entire gamut of inflammatory intensity. It may be anything from a very faint and transitory redness and swelling to the most violent necrosis, with haemorrhage and rapid sloughing (Koch phenomenon). We are very likely correct in assuming also that below the limits of visibility reactions may occur which are so slight that they comprise the outpouring of only a few cells. Sometimes the reaction may be delayed: instead of appearing from six to twelve to twenty-four hours after the application of tuberculin or bacilli, it becomes manifest only from two to four days thereafter. Not infrequently the reacting area presents a centre which is blanched and pallid while the periphery is pink or red.

8. Factors which influence the intensity of the reaction: The most prominent analyzable factors are the degree of allergy at any time and the amount of antigen (tuberculoprotein, tubercle bacilli). High allergy with much tuberculin or many bacilli at a point make for prompt and vigorous reaction.

High allergy with few reinfecting bacilli or low allergy with large numbers may give rise to only moderate or slight reactions. There is one factor, which has never been studied experimentally, but which undoubtedly has a definite influence on the intensity of the reaction of the skin. This is the amount and character of skin pigmentation; for instance, the pigment-free skin of albino guinea pigs reacts much more vigorously than colored skins, from light fawn to black. Another factor which may presumably affect the capacity for allergy is a constitutional one of heredity,—that individual, family and racial variation of native reactivity to irritation which we have already discussed. Since the presence of pigment or the tissues' ability to form pigment is an inherited factor, it takes its place with whatever other qualities make up the hereditary factors of allergy.

Here then is an acquired type of tissue reactivity to tubercle bacilli and its derivatives. Besides the native way of meeting the bacilli rather leisurely, there is the exaggerated and explosive method of allergy which comes to all animals with the development of tubercle. Allergy is thus a specific state brought into being with specific substances and released by specific substances. How and to what purpose does it function in tuberculosis?

As one ponders the various characteristics of the allergic state and reaction in tuberculosis, the forces that bring them into being, the changes which they

themselves set in motion, the modifications which they undergo and the agencies which mould these modifications, the more one is inclined to bring allergy into relation with specific immunity to tuberculosis; particularly if at the same time one happens to be familiar at first hand with the manifestations of allergy and specific immunity as these display themselves in animals of controlled experiment.

For it happens that anatomic tubercle brings about other deep-seated changes in the animal body, besides allergy or specific hypersensitiveness. For twenty years it has been recognized that animals with tubercle can withstand relatively enormous numbers of living virulent tubercle bacilli, as compared with normal animals. That is, animals acquire a specific immunity which is one—and only one—of the elements of resistance to tuberculous infection.

Ever since the discovery of the tubercle bacillus (1882) there have been unceasing efforts to attain active (and passive) immunization against infection through the use of almost numberless derivatives and variants of tubercle bacilli. But competent and unbiased observers are agreed that only one procedure is uniformly successful. This consists in preliminary infection with living tubercle bacilli. In other words, we will not admit to-day that specific immunity ever exists without tubercle in the host.

If we treat nontuberculous normal animals with dissociated derivatives of tubercle bacilli, such as

those contained in the various tuberculins or those obtained in relatively pure state by chemical methods of extraction and cleavage, we can get various responses on the part of the animals in the form of "bodies" detectable in their blood serum or in exudates elaborated by them. Such serum and exudate "immune bodies" or "antibodies" comprise precipitins, agglutinins, aggressins, opsonins, complement-fixing bodies, anaphylactin, etc. Every one of these has been obtained by the method just mentioned, that is, without the intervention of infection with living tubercle bacilli. But we do not find that these animals, even with a high serum content of such substances, display a heightened resistance to infection by living tubercle bacilli, and it need hardly be emphasized that a resistance above the normal is an absolute requirement of any state that we would call specific immunity.

At the same time, we can easily and regularly render animals undeniably immune to infection by producing tubercle in them with living bacilli and yet find that the serum of these immune animals is without the "antibodies" referred to above. We must therefore conclude that whatever their function, and this is thoroughly obscure, it has no direct connection with resisting infection.

Out of a wealth of experiment and investigation of the immune state in tuberculosis have come several features which appear with such uniformity and consistency that we are justified in formulating

them as the laws of specific immunity to tuberculous infection. They may be summarized as follows:

1. Specific immunity exists only in animals which at the same time have tubercle provoked by tubercle bacilli.

2. It first appears about the time of the first palpable development of the foci of infection.

3. It persists, in some degree, as long as infection remains.

4. It diminishes with the subsidence and healing of infection.

5. It increases with the extension and evolution of infection.

6. It probably disappears with the enucleation of all foci.

7. It varies in degree directly with the virulence of the immunizing microörganism; or, otherwise expressed, with the amount and activity of infection in the host.

It is of the utmost significance that the conditions and characteristics of allergy exactly parallel those of specific immunity; and this circumstance is true of allergy alone, among all the specific changes of reaction which may be artificially brought about in animals through the bacillus or substances derived from it. For we find that

1. Allergy is never observable unless tubercle is present.

2. It appears coincident with the establishment of tubercle.

3. It continues as long as tubercle persists.

4. It falls with the retrogression and healing of tubercle.

5. It increases with the extension or repetition of infection.

6. It probably disappears with the eradication of infection.

7. It varies directly with the intensity of the disease, which is in turn dependent, not wholly, but in large measure, on the virulence of the bacilli concerned.

This close and direct parallelism of allergy and specific immunity at once suggests that immunity is a function of allergy. As to the character of the mechanism, set in motion by the allergic reaction to accomplish an increased protection against infection, opinions will no doubt differ, inasmuch as the underlying forces of allergy are as yet thoroughly obscure.

While Koch was making his first investigations with old tuberculin (1890) he observed the operation of allergy at its highest. Without grasping the full significance of what he saw, he put on record how guinea pigs which always tolerated first virulent infections (tubercle bacilli) without immediate visible effect would react violently to reinfections if these were made superficially; how the point of reinfection (skin) would inflame within a few hours, become rapidly necrotic, break down, be cast off

as a slough, and then appear as an ulcer which healed; how, also, animals in which all this occurred suffered no invasion from the bacilli of reinfection, while portions of the same suspension of germs inoculated as a first infection into normal, "control" animals rapidly brought about disease and death of the latter. This rapid ulceration followed by a slough and healing wound at the point of reinoculation has ever since been known as the *Koch phenomenon.*

Koch appreciated the immunity part of the "phenomenon." His idea of the cause of the non-occurrence of generalized infection from the second inoculation was that in the sloughing process the bacilli which he had put beneath the skin were cast out, and, with relatively few or none left behind, actual reinfection was prevented or made weaker. This idea still bobs up in explanations of the mechanism of specific immunity. It cannot be tenable, however; for it can easily be demonstrated that even when sloughing and ulceration do not occur—and this is the usual thing when dosage is small or moderate—reinfection does not "take" or does not proceed far. Again, if reinfection is done by way of a vein, the bacilli carried to internal organs will make slight headway under circumstances where sloughing and ulceration cannot enter into the course of events.

Another view, held by Rist, Paterson and others, is that during the inflammatory phases of the allergic reactions there are released and brought into

play, at the sites of reinoculation, substances which disintegrate and dissolve the bacilli,—so called *lysins*. This has the merit of being a reasonable interpretation and of squaring with our present conceptions of methods by which tissues dispose of living foreign particles. Yet direct scientific demonstration of these hypothetical lysins in tuberculosis has thus far been very incomplete and unsatisfactory.

Personally, I cannot conceive of the allergic reaction going on without the intermediation of some kind of lytic action; yet I am disinclined to accept the lysin hypothesis without reserve and at its full face value until I can exhibit the lysins in a way that is free from criticism, and this I have thus far failed to do.

There is yet another at least plausible view which one may take of the allergic mechanism as it concerns immunity. It embodies a mechanical explanation of end effects, not fundamentally different from the one which I have put forward in seeking for a more exact comprehension of the way in which other phases of resistance were brought about. Although it conceives that actual protection against the spread of infection is afforded by and through certain physical obstacles which the operation of allergy puts in the path of tubercle bacilli and thus impedes their spread, it does not seek out the basic springs of allergy and leaves these to the investigator of biophysical and biochemical reactions. My conception would put the case something as follows:

In a normal, nontuberculous, nonallergic animal, because of the leisureliness of native tissue reaction, tubercle bacilli, when first inoculated, are able to spread over a comparatively large territory and to many remote parts of the body with relative facility. I have shown by experiment how in the guinea pig, after subcutaneous infection, bacilli may reach the centre of drainage of foreign particles, that is, the tracheobronchial lymph nodes, in four days or less. This means that, given sufficiently large initial dosage, bacilli in variable numbers can be carried throughout the body and form many loci of infection (though not necessarily of quickly apparent lesion) before competent tissue reactions (tubercle) are interposed to bar their transit and progress and before the infection has established the allergic state in an animal.

In the allergic animal, on the other hand, reinfecting bacilli, wherever they come to a pause in tissues, are met by an immediate tissue reaction—inflammation—which tends to put a more decisive stop to their progress and limit their activities. In other words, they are more likely to be partially arrested *in situ* and at once; while in the normal animal they are given opportunity to multiply and spread before the latent reacting capacities of the tissues are sufficiently aroused to deal with them effectively.

Or, to state the matter in still another way: The tuberculous allergic animal responds with exaggerated or overreaction to specific irritation and

throws up a barrier against the bacilli much more promptly and actively than normally and before the bacilli can get well under way.

There are studies on the larger effects of pure inflammation in general which lend some color of probability to such a view. Pawlowsky, for instance, has pointed out that an inflamed territory is a fairly efficient impediment to direct infection. If he first inflamed a guinea pig's knee joint with a sterile irritant, such as turpentine, alcohol or quinine, staphylococci which he then introduced into the joint would not disseminate beyond it, although twenty-four to forty-eight hours after the injection of staphylococci into a normal joint he could recover the microörganisms from the blood and organs of the guinea pig. Isayeff has also shown "that the peritonitis by a variety of sterile irritants such as a foreign blood serum, bouillon or normal salt solution, temporarily increases resistance to subsequent intraperitoneal inoculations of bacteria." The refractoriness to infection of inflammations of the type of the chronic leg ulcer is familiar; as is the circumstance that acute septic infections, like erysipelas, are not nearly so prone to settle in inflamed wounds as in those of the type of clean surgical incisions or slight cuts, abrasions and breaks of the surface which exhibit scarcely any inflammatory features.

It may be well also to recall that the end result (or shall we say the purpose?) of every inflammation pursuing a normal, uninterrupted and complete

course is fibrosis, to eventuate in the repair of the injury or irritation which called into action the cycle of inflammation. It is fair to assume that with the very beginning of exudation which initiates inflammation, the secondary response, which will soon follow and be noticeable as fibrous proliferation, also gets under way under the spur of the stimulus —a physical injury, bacteria, or what not. We should therefore expect that in allergy, which is revealed to us as a newly acquired intensification of a native reaction, there are protective elements besides those provided by the sharp exudative features of acute inflammation: there should be in addition an accelerated and exaggerated tendency to fibrosis which, all will agree, is a potent factor in resistance to tuberculosis.

I had always thought that this new capacity for inflammation represented the entire transformation which tissues experienced in respect to allergy, until recently, when more detailed studies showed me unerringly that in the allergic animal there is, if compared with the reaction to first infection, also an earlier response with that type of proliferation which results in the formation of characteristic early tubercle. What is observable upon reinfection is first, an almost immediate acute inflammation, then a fading out of the redness and diffuse oedematous wheal-like swelling, followed by the rapid appearance of nodule which arises in a non-inflamed background. These nodules are the real tubercles and antedate by several days those which

develop in the control animals (given a first infection at the same time). This difference is sharp and not to be mistaken if dosage of bacilli is gauged right: if too many bacilli are used and allergy is high, reaction is so intense and prolonged in the allergic animals that events are telescoped and not unrolled in proper sequence, while in the normals tubercle formation comes into view so early that it approximates the time of appearance in the allergic animals; thus the tendency to prompter proliferation in the allergic may be overlooked. If we view the anatomic response of tubercle as a defensive tissue reaction to foreign bodies, as we have every right to do, we accordingly find that the proliferative or tubercular or resisting reaction is likewise much more active in the allergic animal.

In one respect the allergic reaction impresses the observer as being an exaltation of the native capacity to respond to tubercle bacilli, and, if we view tubercle formation as fundamentally a defensive process against foreign body irritation, then specific immunity would appear as a newly acquired and higher evolution of the body's native way of resisting infection. In accordance with such a point of view, it would seem as though all susceptible animals possess their own definite and peculiar normal reacting capacity to tubercle bacilli; a capacity which is within certain limits uniform for a species and which consists, in one particular, in a given irritability of the body's fixed-tissue cells to bacillary stimulation. It is significant, also, that these cells

will react more vigorously and extensively to large first infections than to smaller ones: the time of first visible appearance of tubercle can be advanced several days ahead of normal, if quite large inoculations are used.

But infection "trains" or "sensitizes" these cells (in our present ignorance of underlying forces it is hard to find more precise words), so that their native irritability becomes greatly enhanced. When, therefore, reinfections occur, these cells react to even very small numbers of bacilli with the speed and vigor that characterize their response to very large first infections. The immediate inflammatory reaction is perhaps the expression of a new attribute—one that is foreign to the normal, nontuberculous animal, although it is true that when dosage of first infection is enormous a rapid outpouring of serum and polymorphonuclear leucocytes follows it. But this is an altogether different thing from the inflammation of allergy, as observation and experiment will show. It is a response to the large amount of protein represented by excessive numbers of bacilli and is comparable to the second outpouring of polymorphonuclear leucocytes which later attends the rapid disintegration of caseous tissue and the formation of pus. It comes on rapidly and disappears just as rapidly.

We begin to flirt with new ideas of the nature of specific immunity as we become more and more attentive to what happens when other acid-fast bacilli are introduced into tissues and as we cogitate

its meaning in relation to phenomena such as we have been describing. The face of all this may be deceptive; but I believe that a search after relations may serve its purpose even though it lead us astray.

If you hunt diligently enough you will find accounts of more than fifty acid-fast bacilli. All except the several tubercle bacilli and the leprosy bacillus are called saprophytic or *nonpathogenic*. But, strictly speaking, there are no nonpathogenic acid-fast bacilli. All so called nonpathogens will provoke tissue change; and that the latter is something more than a mere foreign body reaction, such as attends the encystment of inert particles, is indicated by the response of the body to their introduction with allergy and other biological changes (precipitins, agglutinins, etc.).

It is true that they will not set up progressive disease in mammals: we therefore call the latter natively immune and the bacteria nonvirulent. Yet they will arouse lesion in mammals and must be considered pathogenic to that extent. Their inoculation into normal animals is followed by *rapid* tissue response. Within four or five days, and sometimes two days, local swelling and bubo of adjacent lymph nodes are visible. All changes are much more inflammatory (exudative) than those first following first infection with tubercle bacilli, virulent microörganisms. These changes quickly reach their acme,—as a rule within a week or ten days; and by the end of two or three weeks they have

disappeared and the part has returned to normal. After first focalization, the bacilli do not spread through the body. Unless enormous and repeated inoculations are made the animals remain in good health.

What seems significant is that the native reaction of tissues to nonpathogenic acid-fast bacilli resembles superficially and in broad outline the response of allergic and immune animals to virulent acid-fast bacilli. It is similar to the latter in that it is comparatively rapid and that inflammatory features predominate over proliferative ones. We find that to those germs, which the final issue teaches us to call avirulent, the reaction, the native tissue reaction, is rapid, acute and vigorous, and pathological effects begin by being comparatively florid, soon come to a standstill and rapidly subside and disappear; while to those germs (tubercle bacilli) which experience compels us to call virulent, the native tissue reaction is indolent and comparatively delayed—acuteness and vigor begin only after about two weeks, when, because of the first infection, the tissues have been "trained" to allergy.

We ask ourselves whether the native immunity of animals to nonpathogenic acid-fast bacilli dwells in an inherent vigor of reacting capacity to them; or whether susceptibility to virulent tubercle bacilli is the expression of a congenital inability to meet first infection with the promptness that is necessary to localize the germs within narrow limits and prevent their decisive multiplication. Infection

with virulent bacilli endows animals with relative immunity, but only when and after their bodies have taken on new powers; after their tissues have been trained, as it were, to behave in a way that resembles their conduct toward saprophytic acid-fast bacilli,—to react with celerity to fresh invasions by tubercle bacilli and to substitute, in a measure, the speed of exudative (inflammatory) response for the leisureliness of proliferation.

We have also to deal with another phase of specific immunity and of allergy which must undoubtedly be of great importance in any infection in which there is a more or less continuous migration of germs from one part of the body to another or many repeated acts of infection from without (*exogenous* infection) or from parent foci within (*endogenous* or *autogenous* reinfection).

Broadly speaking, in any process of active immunization there occurs a variable incubation period after a first application of immunizing agent (*antigen*) and then a rising curve of increased resistance (immunity) to the specific germ of infection. In time this curve reaches a certain maximum or high level (*plateau*) which may continue for a longer or shorter time. If the application of antigen is repeated during the period of immunity, there is an immediate and very sharp drop in the animal's resistance to the particular substance. Resistance may fall to a point which is lower than the native resistance of the animal; or, to put it another way, the animal's susceptibility may for a space be

unusually and abnormally great. In the course of specific immunity, therefore, we meet with the paradox that at certain times and under the repeated influence of the immunizing agent, resistance is less than in the normal, nonimmunized animal. The phenomenon is well known and is perhaps best known as the *negative phase* of immunity. It can be shown that reinfections made during the negative phase are particularly dangerous. This period of negative phase lasts from a few hours to several days, and is then succeeded by a much more rapid rise of immunity than before and by an immunity that goes to a still higher level.

Allergy is similarly responsive to various influences. We have already seen that the reacting capacity of the tissues (skin) of tuberculous man and animals is blunted by such events as the general reaction to tuberculin, pregnancy, measles, influenza and other febrile diseases, acute tuberculosis, terminal tuberculosis, and the last cachectic stages of exhausting illnesses of many kinds. A child known to react to a Pirquet application of tuberculin in health will fail to react during the clinical course of measles, or if stricken with tuberculous meningitis or acute generalized tuberculosis. It has generally been taught that in the latter affections and the agonal stages of many diseases allergy is lost completely. My own experimental observations and recent work by Happ and Casparis lead me to believe that this is not strictly true, and that what is more likely is that every person or animal with tubercle, no

matter what the constitutional condition, can be made to react to tuberculin, provided enough tuberculin is given. In other words, there may occur a very great diminution of reacting capacity, but the latter is never entirely gone as long as tubercle remains.

A satisfactory explanation of why allergy should undergo these modifications has not yet been advanced. Most theories proceed from what may be called the "antibody exhaustion" hypothesis. It is held that the specific antigen (immunizing or allergy-provoking substance) stimulates the body to elaborate specific antagonistic substances, which pass under the name of "antibodies" or "immune bodies." An actively immunized or allergized animal will possess an excess of these and upon the introduction of new antigen (tuberculin or tubercle bacilli) there occurs a reaction between units of antibody and antigen which results in the inflammatory reaction of allergy. Florid or very progressive infection provides antigen to an excess that at last stimulates the body to exhaustion—to that point when it can no longer respond with antibody; or the excess of antigen "uses up" all available antibody and thus exhausts it. In either event, there is no antibody left to react with whatever antigen (tuberculin) we may apply in these cases, and no reaction results. In nontuberculous affections, the resources of the body have enough to do in combating whatever disease or condition is menacing, and for this reason can devote none of their powers to respond with

specific antibody to an antigen of tubercle bacilli: here again, there is an exhaustion or a nonproduction of antibody and the application of tuberculin passes without reaction.

I have never been able to entertain the "antibody exhaustion" view. It has always been my experience that, no matter how refractory to tuberculin a very ill animal might be, it would always manifest some reaction to a large enough dose of tuberculin; and it was impossible for me to reconcile this plain observation with any idea of an exhaustion or nonproduction of specific reacting substances in the animal. It appeared to me rather that under the influence of any condition which brought about great or sudden depression or exhaustion of bodily (constitutional) function, the normal reaction of the tissues to any and every irritant was altered. Highly anaemic tissues, for instance, will not respond at all with the same characteristic inflammation to a bruise or a cut or a burn as will normal tissues. Typical bodily reactions are conditioned on two factors, namely, the integrity of the stimulus and irritant and the integrity of the mechanism concerned in reacting. As I conceive it, whatever gives rise to the inflammatory response of allergy is a noxious degradation product of tubercle bacilli (or a derivative) which results from an antigen-antibody reaction and is an irritant for tissues. If the body is functioning normally in respect to response to irritation the result will appear in the acute inflammation with which we are familiar.

If, for any reason, specific or otherwise, function is depressed or abnormal, there can be no characteristic tissue response, even though an antigen-antibody reaction occurs and gives rise to the substance or substances capable of arousing inflammation.

This opinion is borne out by an incident which I have already mentioned, namely, the failure (inability) of the skin of acutely ill guinea pigs to react to first infection with tubercle bacilli with the formation of characteristic nodular tubercle: in this case animals lose their native capacity to react typically. I have also had brought to my attention the following case which is highly significant:

A child in the service of Doctor John Howland of the Johns Hopkins Hospital was sick with what was clinically generalized miliary tuberculosis, and failed to react to several Pirquet tests. It was also profoundly anaemic and for this reason was transfused. After the transfusion it reacted vigorously to new Pirquet tests, to which the former nonreacting areas also at once responded with inflammation. The child died and at autopsy was found to have generalized miliary tuberculosis.

In other words, a transfusion of blood brought an abolished reacting capacity up to normal. All experimental efforts to transfer the antibody of allergy by injecting the blood serum of an allergic animal into a nonallergic one have turned out negatively. We cannot therefore conclude that in the above instance we put into the sick child's body by transfusion a reacting substance which it lacked. We must assume that it possessed this

all along and that when the first Pirquet tests were given an antigen-antibody reaction went on in its tissues and gave rise to the inflammatory irritant. We must assume further that it failed to react with inflammation to the irritant because its tissues' capacity to react had been disturbed (depressed?) by disease. A transfusion of normal blood restored for a time this ability.

Tuberculous infection assumes and gains importance and momentousness as it spreads within the body. This spread is nothing more or less than reinfection from within. As soon as first tubercle is formed, its possessor becomes allergic and specifically immune. Therefore, after about ten days from the first infection all new focalizations of bacilli within the body take place in allergic and immune soil. But it must be kept in mind that in many instances the conditions of such reinfections must be vastly different from any that an investigator has yet reproduced by experiment or any that he conceivably might reconstruct. In nearly all experimental work on immunity and allergy, if we apply antigen repeatedly, we space our new injections and inoculations so that they fall within the period of high immunity and allergy. In the course of many natural infections reimplantations of bacilli are taking place at many different times: there may be sufficiently long intervals so that new infections occur when immunity and allergy are at their peak; or, presumably, reinfections may be repeated so frequently and at such short intervals that some fall within the period of negative phase

and anergy. If they occur during the latter they come upon the tissues at times of depressed or no reaction (tissue reaction) and, therefore, when new barriers of inflammation or proliferation will be either absent or inefficient. After negative phase and anergy pass, after the measles or acute febrile disease is over, tissue reactivity comes back, perhaps with intensification, yet it is then called upon to meet the irritation of germs which have spread to new points or have been transported out beyond the boundaries of old foci to enlarge these or may have perhaps multiplied while reactivity was depressed or in abeyance.

Something like the above is my present very rough and very imperfect conception of the mechanism of allergy and specific immunity. The gist of it is that immunity and allergy are both specific antigen-antibody processes which, through their operation, originate and yield a stimulating or irritating product which is specific. But the capacity of the body to react is not specific: it is the same capacity which will respond to any comparable irritation with the same pathological changes—that is, acute inflammation, heightened fibrosis and accelerated tuberculoid proliferation. In depression or exhaustion states the tissues cannot react typically to any irritant, and therefore they respond only feebly or not at all to the application of antigen. The actual mode of protection against the spread of infection probably does not differ fundamentally from the native resources of resistance which the

body possesses: through immunity and allergy the tissues' native capacity to ward off and wall in bacilli is simply exalted in greater or less degree. No tuberculin or dissociated product of tubercle bacilli has yet been shown to protect or raise native resistance against infection, that is, implantation of tubercle bacilli: only living tubercle bacilli, capable of arousing tubercle, exert this effect markedly. Therefore, no tuberculin can be looked upon as being a prophylactic or preventive agent against a *first* infection. On the other hand, tuberculin has antigenic properties in that it will affect foci already present (focal reactions) or noninvolved tissues (skin, etc.) of tuberculous animals. By virtue of these qualities tuberculin may set in motion processes which may result in *apparent* immune effects, a phase of resistance which must await discussion later.

It remains to pass in review and examine the effects of resistance, particularly those of allergy, as these are displayed in the natural evolution of tuberculous infection and disease. I have long thought that an understanding of allergy and its proper application will lead to a better appreciation of much that has been obscure and that it will resolve features that have been confused and chaotic into fewer and simpler concepts.

Allergy undoubtedly furnishes the key which bids fair to unlock the outstanding riddle of tuberculosis—the mystery which so baffled early observers and so long delayed a more rational concept

of the disease; that led Virchow into the quagmire of the duality dogma and pushed Niemeyer to that absurd though logical conclusion of Virchovian doctrine—that "the worst thing that can happen to a consumptive is that he become tuberculous." How understand the mystery of the enormously multiplex and multicolored pathological background as all parts and variations of one and the same disease due to a single cause—how understand it before the cause could be known? How explain it after the single cause, the tubercle bacillus, lay bare? Through what variables is there produced a pathological framework which may run the entire scale from almost pure tumor formation to purest inflammation, with all proportionate combinations of these elements, and punctuated with effusions of every type, the deposition of salts and the irregular formation of cartilage and even bone?

Well, all this has had its explanations. It is—so it has often been maintained—the virulence of the bacilli concerned which will determine the type of pathological response in particular cases. Almost innumerable virulences have of necessity been postulated to explain how almost innumerable anatomic conditions may be set up. Yet the net result of many studies on virulence has been to emphasize all the more for tubercle bacilli a fixity and constancy of bacillary type and qualities which is almost unique among the microörganisms of disease. Differences have been described, it is true, but always woefully insufficient to throw light on

differences of anatomic effect. Again, no investigator has ever been able to correlate distinctive features of anatomic change in particular cases with differences of bacillary attributes.

It has also happened that the realm of pathogenic bacteria in general has been drawn upon in attempts to understand better why caseation and liquefaction and inflammation and acuteness and so forth in one case and not in another. Tubercle bacilli of themselves, so many have said, can go just so far in provoking the anatomic changes of the disease tuberculosis. They will arouse the production of nodular tubercle and perhaps take part in the formation of that peculiar type of tissue death, caseation, though not all will admit their part in the latter. When, however, it comes to disintegration and liquefaction of tissue—the formation of pus—and those inflammatory features which make tuberculosis acute and are expressed in the spitting of blood, the hectic fever and the drenching night sweats, then other germs—the pus-formers—must step in to bring about all this. Hence, our "mixed infection" view of tuberculosis which has been quite popular. It is really nothing more or better than the doctrine of Virchow and Niemeyer put into the jargon of a later day. It attempts to explain bacteriologically what the men of sixty years ago illumined morphologically. It has a single circumstance to support it and this a mere association without proof of any causal relationship, while all positive facts and many negative ones are against it.

The "mixed infection" concept has attracted attention and support because germs of known pathogenic types have been found in the secretions of known tuberculous people and also in their tuberculous foci. It has gained in force because some features of diseases, due to these "secondary" microörganisms alone, resemble some features of the more acute types of tuberculosis. At a loss to explain how a single etiological agent, the tubercle bacillus, can bring about so many variations of disease, some students have derived from the association mentioned a synthesis of action and effect.

Now the occurrence of pathogenic germs other than tubercle bacilli, in secretions such as the sputum of the tuberculous, of itself certainly need not mean that these germs are contributing to the disease represented by the tuberculous process. Nor need it mean that they are setting up another disease, apart from the tuberculosis, though this may and frequently does occur in the tuberculous. The occurrence of streptococci or pneumococci in old tuberculous foci in the lungs themselves, if this can be demonstrated at autopsy, cannot without other evidence be interpreted as meaning that they set up tissue change or took part in the clinical tuberculosis.

Spontaneous pneumothorax is usually the result of a tear in a diseased part of the pleura overlying a pulmonary cavity. For the most part, such cavities are old and would present the ideal tuberculous foci in which other germs might flourish. If

mixed infection, in the real sense of infection (not of contamination or association of other bacteria), were at all common, we should expect regularly to find other germs than tubercle bacilli in the exudates which accompany spontaneous pneumothorax; for all the pus-forming cocci are rapid "growers" compared with tubercle bacilli. It is remarkable, no less than it is significant, that, when these pneumothorax exudates do contain bacteria, in the very large majority of cases only the tubercle bacillus is present.

But, altogether apart from such negative evidence, tubercle bacilli alone can bring about practically every type of anatomic change to be met with in tuberculous infection. Thoroughly controlled experiment will demonstrate beyond the slightest ground for adverse criticism that necrosis, every kind of acute and chronic inflammation, and pus will follow tuberculous infection. No one questions that the ordinary cold abscess with pus is brought about through the action of any other germ than the tubercle bacillus; or the psoas abscess (before operation) which may communicate with a caries of the spine; or the kidney abscess which sheds off tubercle bacilli into otherwise sterile urine. Then why assume that the lung abscess of tuberculosis needs another germ for its formation?

Experiment will clearly disclose this: That first infection during its first few days practically always proceeds in the uniform manner which I have already described, no matter what the dosage of

infection; that the process involves largely the fixed tissue; and that the result is discrete tubercle. But after animals have been made allergic, pathological response to reinfection can be an enormously variable affair; and, as has also been mentioned before, it must be remembered in this connection that shortly after first infection has occurred the host becomes allergic because of it, and extension of infection within the host will take place in allergic soil.

In any series of infections and in natural infections the *dosage* of bacilli can alway be a variable. But in experiment we can make dosage a constant. We can make the type and strain of germ also a constant. We can also make the method of inoculation a constant. In other words, we can readily perform infections in which every factor concerned with the germ is the same for all animals inoculated: we can give a large number of the latter exactly the same amounts of the same suspension of living bacilli in the same place at the same time. What will be the result in several animals?

It all depends on the animals. If the animals are normal and are receiving a first infection, and our technique is good, the results are roughly similar. But if they are allergic they may vary greatly.

We may use guinea pigs of various degrees of allergy, depending on original dosage and time since infection, and these we may look upon as variables. The response which we may observe will be extremely diversified, depending upon the degree of

allergy at any particular time. There may result anything from mild inflammation to extensive and violent necrosis, followed by sloughing (if the inoculations are made into the skin). In all the allergic animals the immediate changes will also be quite different from those observed after infection of the normal animals. They will tend to be inflammatory. Intravenous inoculations may result within a few days in as purely exudative pneumonias as one ever sees, with interstitial tissue apparently thoroughly passive and air cells filled with serum, fibrin, leucocytes and some red blood cells. I have, on occasion, as a result of an inoculation of this kind, seen the leucocytes, which filled the alveoli, crammed with tubercle bacilli. Now these bacilli were put in by a vein a few days earlier and were no doubt carried out into the alveoli with the exuded leucocytes. But observations like these have made me wonder whether, after all, ulceration of a pulmonary focus is always necessary for the appearance of tubercle bacilli in the sputum—any more than it is necessary for the occurrence of pneumococci in the sputum of lobar pneumonia; whether, in acute tuberculous pneumonia, bacilli might not gain the sputum by being carried out into the air cells with the exudate. Of course, if reinfecting dosage is also variable, the results in allergic animals can be even more diversified.

Is the peculiar necrosis, the coagulation necrosis of Weigert, the caseation, of tuberculosis an allergic effect? It may occur with extreme rapidity, as now

and again happens when the contents of cavities are discharged into midlung; when, in other words, large numbers of bacilli are brought to bear suddenly on highly allergic soil. Or it may develop slowly, in small foci, where a few bacilli are disintegrating slowly, and a gradual sensitization and intoxication are taking place *in situ. Tuberculin and tubercle bacilli are necrotizing for tuberculous, that is, allergic animals;* they have no such effect on normal, non-tuberculous animals;—as can easily be proved by skin injections and inoculations. We may also recall the Arthus phenomenon, that is, the rapid appearance of necrosis after a second injection of horse serum into the same area of the skin of a rabbit where horse serum had been injected before. Although this particular question has long engaged my attention, I shall not attempt to answer it. In passing, however, it may be added that the idea that caseation, like white infarct, is a result of tissue anaemia, occurring in a thrombosing infection and in avascular foci, is very vulnerable. The frequent early occurrence of caseation in very minute miliary tubercles, the centres of which must surely be in nutritional communication with surrounding healthy tissue, is against it for one thing.

As I conceive it, every inflammatory feature of tuberculous infection is a manifestation of allergy—of immunity; and will begin to appear only after a primary infection has taken place. I think we may safely say that every acute tuberculous process is the result of reinfection in tuberculous soil—either

a reinfection that is set up in an existing focus or a reinfection from an existing focus into new territory. It is plain that serous membrane disease—tuberculous pleurisy and peritonitis with and without effusion, tuberculous hydrops of joints, tuberculous meningitis—must be reinfection phases, in the sense that they represent extensions or metastases from foci elsewhere in the body. Their acuteness and severity and the amount and character of their effusions will depend on degree of allergy and size and concentration of dosage at the time of reinfection. Acute tuberculous pneumonia is most frequently met with lower down than the summit of the lung, and is usually brought about by spread of infection from older pulmonary foci in upper lobes; an origin from ulcerating root lymph nodes, discharging infection into the larger bronchi, must be a much rarer event. Miliary tuberculosis, localized or generalized, another acute type, is always the result of reinfection from older foci. In miliary disease we find many small and discrete areas which, as experiment will disclose, show acute inflammation in their early stages, but in which the inflammatory features may have subsided by the time death ensues and the tissues are observed at autopsy. Miliary infection arises from the widespread and scattered distribution of bacilli to very many loci, when very small numbers of bacilli exert their effects on tissues of variable allergy; while many areas of acute tuberculous pneumonia result from the aspiration of material from older foci, and are

large and massive because large numbers of bacilli are brought to bear within a comparatively small compass. In chronic apical tuberculosis of ordinary type, that is, chronic infiltrating tuberculosis, it is likely that tubercle spreads with extreme slowness and by short excursions of bacilli by way of lymphatics, as well as by growth of tubercle by concentric apposition. Fibrosis is always fairly well developed; and bacilli which set up fresh foci are relatively few at any one time. The infection may proceed with only slight pneumonic features, inappreciable to ordinary physical examination and too insignificant to reach a level of clinical acuteness.

Tendeloo discusses at length the importance and nature of what he calls the collateral inflammation of tuberculous processes. He points out how tissues may be acutely struck with inflammation where tubercle bacilli localize, and throughout a wide territory, which extends beyond the actual place of bacillary focalization; and how the peripheral inflammation may rapidly subside, to leave only the "nucleus" of infection—the bacilli-containing centre —which may then go on to caseation or fibrosis or both. There is also no doubt that the entire process may undergo complete resolution, with restoration to normal, as I have frequently observed in experiments with immunized guinea pigs.

Tendeloo's conception of this type of infection, pathologically, is that it is determined by dosage and virulence of bacilli; and he nowhere mentions tissue allergy as being a factor in its production.

Yet it is exactly comparable with what we notice when we experimentally reinfect the skin of a tuberculous or allergic animal and fail to observe when we infect the skin of a normal, nonallergic animal; and there is no doubt that Tendeloo's collateral inflammation is an expression of allergy.

We would repeat, therefore, that *the acute pathological phases of tuberculosis always mean reinfection;* and again refer to the fact that from about ten days on, after a first infection, an animal becomes allergic by reason of this primary infection and is then capable of exhibiting acute processes, provided direct extension of infection or reinfection to other parts of the body occurs. We would also emphasize that in allergic animals reinfection may be caused by so few bacilli that the allergic reaction is so mild as to pass unnoticed, or reinfection may occur after long periods of quiescence, as undoubtedly happens frequently in human beings, when allergy is comparatively low.

Since the clinical features of disease are for the most part but expressions and reflections of underlying anatomic change, through the derangement of function which these bring about, we may now go one step further and suggest that *acute clinical tuberculosis is always the expression of reinfection.* If a man falls suddenly ill with the more intense features of the disease it means that there has been a rapid fresh extension or metastasis of infection from already present foci, whether these latter were

or were not known to exist. I have yet to see an animal become acutely ill following a first inoculation of living, virulent tubercle bacilli—even of excessive doses of a milky suspension introduced by a vein. I have yet to observe a tuberculous animal *not* show acute illness following a similar introduction of smaller doses of reinfecting bacilli.

This brings us at once to the matter of intoxication which makes up so large a part of the clinical side of tuberculosis and which expresses itself in so varied a way. The subject is intricate; but it is at the same time so important that it must receive some attention here. Intoxication brings on the constitutional symptoms of tuberculosis. It is these—their occurrence, their vigor, their responsiveness to outside agents—which become so prominent in the diagnosis and prognosis of pulmonary tuberculosis and in any estimation of activity or latency of infection.

Any consideration of the nature of intoxication must revolve around the primary question of what causes it in tuberculosis. No evidence has ever been forthcoming that the cause is a specific toxin, in the accepted meaning of the term, for no one has ever satisfactorily shown that any constituent or product of tubercle bacilli acts as an essential poison, in the sense that it will adversely affect the well being of normal animals. Yet excessively small doses of derivatives of tubercle bacilli or small numbers of intact tubercle bacilli themselves will set up symptoms of violent illness in tuberculous animals.

We find, in broad outline, intoxication occurring under two very different and distinct conditions. It appears spontaneously during the natural course of tuberculous infection, either with or without the contributory influence of unusual environment. It is also, as I have said, brought on artificially by the action of tuberculin, a specific product of the bacilli, or by the living bacilli themselves. So far as can be determined by observation of symptoms, it is likely that the intoxication of ordinary active tuberculosis and that of the general tuberculin reaction do not differ in kind, however much they may vary in intensity and duration.

In my discussion of the relation of tubercular investment to symptoms, I pointed out how the symptoms, in other words, the intoxication, of ordinary tuberculosis must surely develop from the bodily absorption of materials from tuberculous foci,—of elements which comprise the products either of bacilli or of whatever cells enter into the constitution of foci, in variable proportions and in a variety of physical and chemical states, contingent upon the processes of proliferation, exudation, degeneration and repair which may be going on at any time.

There are also the best of reasons for believing that the intoxication of the general tuberculin reaction results in large part, if not wholly, through the operation of the same proximate mechanism. These reasons are (1) that the general tuberculin reaction cannot be evoked in nontuberculous animals,

(2) that it is always accompanied in a tuberculous animal by a focal reaction, (3) that it does not occur in the latter unless focal reaction takes place and (4) that close observation of accessible foci will demonstrate unerringly that focal reaction begins before the first manifestations of the general reaction.

In several other contributions I have already reported the results of experimental studies which lead me to believe that the intoxicating substance of tuberculosis is in large part a nonspecific material and not necessarily derived from the bodies of tubercle bacilli. I am led to believe that any tissue products, normal or abnormal, when thrown into the circulation in excess in unit time, will poison an animal. Deep-seated chemical changes (ferment action, cleavage, etc.) are very likely going on in tuberculous foci with greater or less rapidity all the time. In the natural evolution of infection, intoxication is to a great extent a nonspecific process, brought about by the absorption of focal materials in amounts large enough to produce symptoms. But if tuberculous animals are given tuberculin in overdose or suffer reinfection with large enough numbers of bacilli, then intoxication is set in motion through an immune or allergic process, although again the actual poisonous material absorbed is largely nonspecific and does not differ from that which causes the ordinary intoxication of tuberculosis.

Because they are allergic, tuberculous foci react with inflammation to new implantations of tubercle

bacilli or to applications of tuberculin. This reaction is an immune phenomenon. Its physiological effect is to inflame the foci of tubercle and the tissues surrounding them and this inflammation contributes to the dissolution of focal products and to the facility with which they are absorbed.

In the vast majority of cases of human tuberculosis, reinfection, extension, metastasis, proceeds with so few bacilli concerned that no appreciable acute explosion occurs and relatively slight new lesion results. Such instances, the commonest events in human tuberculosis, do not resemble what we usually bring about in experimentation. But when large amounts of material are let loose suddenly over a single area or are scattered broadcast, then we begin to see approximately what we observe in our laboratory animals following our ordinary methods of study. It is such events that provide for us our clinical cases of acute tuberculous pneumonia and generalized miliary tuberculosis.

In both these types of clinical disease, previously healthy men may fall ill abruptly; sometimes in miliary tuberculosis even with a rigor. Intoxication of varying degree dominates the entire early phase of the illness; at first localizing signs are few or they may be entirely absent. The patients may experience an early clinical course which in essentials does not appear materially different from that observed in tuberculous guinea pigs or rabbits reinfected with moderate doses of living bacilli intravenously. Within a very short time—four

to six hours—such animals become very ill, with fever, dyspnoea and thorough failure of muscle tone, and their appearance is one of extreme misery. Many die in from twelve hours to two days after reinfection; the survivors slowly come back to their previous health.

If we section the dead animals we get the clue to what has been happening; indeed, where tubercle existed the whole organ may be inflamed. In other words, foci have been "reacted" by the reinfecting bacilli (just as they would be "reacted" by tuberculin). But there may, in addition, be many other acute changes throughout the body: the lungs and other organs may have many small, sometimes confluent, areas of acute inflammation, sometimes even with haemorrhage, where bacilli in sufficient numbers have embolized.

In such animals there is no doubt that the acute illness, the intoxication, is caused in part by the absorption of the same focal substances which arouse the symptoms of ordinary tuberculosis; in these cases under the influence of acute reaction brought about by reinfecting bacilli. The symptoms of reinfection are an intensification, as a rule, of those of the chronic case. They no doubt have causes besides the one just mentioned. There may be a rapid outpouring of inflammatory elements wherever new bacilli lodge, and part of the intense intoxication may be due to absorption of these freshly exuded materials, as may conceivably happen in the lobar pneumonia which comes on abruptly, with rigor and

prostration, with a precipitate formation of congestion and inflammation. A certain amount of the intoxication may also be caused by the absorption of products originating from the rapid destruction and dissolution of reinfecting bacilli lodging in hypersensitive soil. But I am inclined to ascribe a comparatively small part of the intoxication to these particular materials, especially when I think of several features of intoxication in human tuberculosis.

We frequently meet, for instance, with few symptoms of intoxication in patients who are expectorating unusual numbers of bacilli; in some cavity cases, for example. In these, of course, we may be dealing with well walled off cavities which permit but slight absorption of focal material which is, besides, being readily evacuated: even though it could be shown that bacillary elements are the actual poisonous substances, we would understand why such patients present few symptoms. On the other hand, some patients with rapidly caseating and disintegrating tubercles labor under profound intoxication; yet, as is well known, their lesions may contain few bacilli. As Koch pointed out long ago, bacilli, again, are not a prominent feature of certain stages of generalized, miliary tuberculosis, a condition marked clinically by great intoxication, and pathologically by innumerable foci of cellular proliferation and exudation with relatively slight focal investment.

At all events, there can be little doubt that the immune or allergic state exerts marked effects on the symptomatology of tuberculosis. It is brought into action whenever new localizations of bacilli are to be dealt with. The tissues react vigorously with anatomic results which contribute to the illness. Acute inflammation arises where the new bacilli focalize for the time being, and something is released from the bacilli which may in addition react with existing, older foci, inflame these and set up those conditions which promote focal absorption; hence, sudden access of intoxication or intensification of whatever symptoms have been present. If there is anything essentially poisonous in the bacilli themselves and this is absorbed, it probably contributes but slightly to the intoxication.

For the broad and indisputable fact remains that the normal nontuberculous animal tolerates living tubercle bacilli or their derivatives without illness, while the tuberculous animal, made immune and allergic by its infection, is at once profoundly affected thereby. The symptoms of tuberculosis, particularly if they are intense and acute, must therefore be regarded as immune phenomena. They arise out of the effort which the body makes to resist infection, to meet it with unusual vigor, to check the advance of the bacilli and to destroy these. In the struggle the patient may die, sacrificed to the performance of the special function which the body is exercising at the time. Nature is always lavish in responding to an immediate need. Pleu-

risy with effusion, at bottom, is without question a phase of resistance to reinfection; so is the inflammation of tuberculous pneumonia, or the exudation of even tuberculous meningitis. The fact that the body may overdo or that the combat goes on in a peculiarly dangerous location, so far as the general economy is concerned, and that the patient may be made gravely ill thereby or even be deprived of life, detracts nothing from the certainty that it is his resistance which is fashioning the catastrophe. If a hundred normal guinea pigs are subjected to a given dose of virulent tubercle bacilli, every one will bear the infection at first as though nothing had happened; for several weeks they will appear as lively and as unaffected as ever. But in from two to three months every one will have died of generalized tuberculosis. If, however, a hundred guinea pigs with slight and well-borne tubercle are given similar doses as reinfections, all fall ill almost at once and perhaps a number will die within two or three days; but all of those which survive will be alive two or three months afterwards and will have overcome their second infection—the infection which was ultimately fatal when it was made to be a first infection. When we get to speaking of a patient who is becoming acutely ill with tuberculosis as a person who is losing his resistance we are being misled by appearances and are speaking outside the facts—at least, if our criterion of facts be that which can be sharply demonstrated, and if our gauge of resistance be an increased ability to ward off or to

localize infection. There are exceptions; but it is incontrovertible that in infections vigor of symptoms goes hand in hand with resistance. For the time being, the patient with "stormy" illness may be the sickest pneumonic and his exceptional derangement of function may kill him; but it is the more comfortable patient with low reacting capacity, with depressed leucocyte count, that we are always hopeless about. We have learned that he always dies. He really has no resistance and his placidity of reaction shows it.

By way of recapitulation I may put my view of the intoxication of tuberculosis as follows:

The course of active tuberculosis in itself represents, no doubt, a wellnigh irresolvable complex. There are no doubt cases, many of them, which during the entire period of activity evolve and recede without bacilli ever being conveyed to points outside of the active focus and setting up reinfection elsewhere. There are other cases, again many of them, in which it is plain that massive reinfections, localized or disseminated, are taking place. There are still others, perhaps the majority of cases, in which the infection progresses through reinfection, occasionally or frequently repeated, by comparatively few bacilli, which have been transported by way of lymph or blood or visceral duct.

In all three types of cases intoxication will take place from nonspecific focal materials. In the first type, constitutional symptoms will appear whenever there arise those conditions of focal

investment or physiological activity, or both, which will make possible the absorption of sufficient focal materials. In the second type there will also be this type of intoxication; but intensified and acute because of the sudden release of large amounts of focal material set free and absorbed during and by reason of an immune reaction which results in focal inflammation, a reaction which is followed by the implantation of bacilli at new places in the body (in other words, a tuberculin effect). There is, in addition, an acute intoxication, set up by the rapid inflammation of reinfection *in situ* and in part perhaps by products arising from the rapid degradation of bacilli. In the third type there will be nonspecific focal intoxication, with the acute type added whenever reinfection is extensive enough to call forth symptoms; for, just as we find that there is a limit of tuberculin dosage below which effects on the body are inappreciable, so there is a line of reinfection below which its immediate effects will proceed without being detectable.

I must believe further that acuteness of constitutional symptoms always means reinfection, that is, infection rapidly or suddenly enlarging its boundaries and encroaching upon and extending into healthy tissues, or infection conveyed from one point to another. It is always an expression of the allergic or immune phase of tuberculosis. Experimental evidence allows no other opinion and clinical experience abundantly bears it out.

In bringing this account of resistance to tuberculosis to a close, I may attempt a brief explanation of the action of tuberculin, in conformity with the point of view that has colored this entire concept of resistance. When speaking of tuberculin, I have in mind the many derivatives of tubercle bacilli (usually dissociated products) which go by this name.

At the end of my analysis of the nature of resistance I stated that tuberculin has no immunizing action in the sense that it will protect against infection. Since Koch's first astonishing claim in 1890, and even before, if we recall the earlier work of Héricourt and Richet, Courmont and Dor, Grancher and Martin, and others, there has been no lack of experimenters to maintain the contrary. The literature of tuberculosis teems with recitals of the successful protection of animals of all kinds against tuberculous infection with many different products of tubercle bacilli. But it is surely not unfair to any claimant to suggest that the lapse of time with its accumulated trials and experience of the various methods has not borne out the promise originally held forth for a single bacillary constituent. Today, if we are unbiased, we can admit successful immunization by only one method and that is through living bacilli, through preliminary infection.

Yet, after infection is established, tuberculin at once begins to exhibit marked effects on the body. Moreover, its action at bottom is seen to be a specific one, even though all steps of the extensive and intricate mechanism set in motion by tuberculin

need not be specific. Because of an alleged immunizing influence, it has long been used in the treatment of established infection, with the idea that, in some way or other, it endowed the infected body with added powers of resistance. All clinical experience leaves no doubt that through the intelligent and repeated application of tuberculin an infected body's tolerance to it can be enormously increased: this fact has strengthened the idea that tuberculin is a true immunizing agent. At the same time unchanged susceptibility of the tuberculin-treated, nontuberculous animal to infection has prevented our accepting tuberculin as a specific raiser of resistance. If tuberculin is not an active immunizing agent, then our task is to explain how the tuberculous body's tolerance to it is brought about or why an increased tolerance to it accompanies its repeated use.

It is well understood that in practice tuberculin cannot be used indiscriminately. Clinical experience and controlled experiment have both taught us that it is not safe for all tuberculous animals. Out of our experience we may formulate that it is altogether harmful in acute disease and that it is applicable in direct proportion as the symptoms of intoxication are in abeyance. We have come to lay down such general rules as that it should not be administered to patients with temperature over 100° or with other evidences of more than mild clinical activity.

The reason for all this must be evident. It is a specific quality of tuberculin that it enters into

reaction with *tuberculous* tissues and with *non-involved tissues of tuberculous* animals. Its intensity of reaction depends on the allergic irritability of both types of tissues. This allergic irritability depends on the activity of the existing infection. This activity depends largely on focal investment, that is, the relative fibrosis of whatever tubercle is in the body. With poor or insufficient fibrosis there will be more activity, higher allergy, and greater susceptibility to tuberculin. As fibrosis becomes better, susceptibility to tuberculin will diminish; as foci stand more "naked" or new foci are established, susceptibility will increase. *In other words, as tubercle recedes tolerance to tuberculin rises; as it progresses, tolerance declines.*

It is also true that the facility with which tuberculin will enter into reaction with foci depends on the amount and character of focal fibrosis; that is to say, that foci with more and better fibrosis will withstand larger subcutaneous injections of tuberculin without reaction than will processes with less or poor fibrosis. At the same time, the vigor of reaction is expressed largely in intensity and extent of focal inflammation. Too much may be bad for an animal already laboring under very acute or active infection. But this inflammation can, of course, be anything from transient hyperemia to violent exudation and necrosis. In mildly active and sluggish processes a certain amount of inflammation may be of service; for it may stimulate the fibrosis, which always follows it, just enough to

close in completely what were insufficiently invested foci.

Now, our guide of so-called tolerance to tuberculin is the ease with which a reaction, usually a constitutional reaction, to it can be induced. Since the constitutional reaction is the effect of the focal reaction, this is only another way of saying that our index of tuberculin tolerance is the responsiveness of focal reaction. As the latter remains absent with increasing doses of tuberculin it means, if a focus has never reacted, that we have not yet reached the dose of tuberculin large enough to "react" it. If it has reacted to a small dose and then fails to react as we continue to give larger and larger amounts, it means that the foci are becoming better fibrosed. If the successive applications of tuberculin fail to throw the foci into vigorous reaction, they may, by inducing very mild and unnoticeable reactions, contribute to the fibrosis, the healing, through these repeated mild stimulations. It may be impossible to demonstrate all this in hidden and inaccessible pulmonary tubercle, but it can be followed at every step in such observable infection as that of the rabbit's eye or guinea pig's skin.

Experiments on anaphylaxis disclose that the nontuberculous animal cannot be made less sensitive to tuberculin through repeated application of it. It becomes more sensitive, or *hypersensitive*, as we say. There is no rigidly analyzed evidence to lead us to believe that the *body* of the tuberculous

animal can be made less sensitive to tuberculin through repeated and graduated dosage. To repeat: *Tuberculin effects on the body which we observe in practice are focal effects. Tuberculin action that manifests itself to us is a focal action. Tuberculin tolerance is focal tolerance.* Tuberculin tolerance is increased as focal tolerance to it rises, and tuberculin can contribute to this enhancement by contributing to focal fibrosis through mild stimulation. After our long discussion of the part which focal investment plays in resistance, the application of this concept to resistance where it touches the pathology and symptomatology of tuberculosis is plain.

I leave this analysis of resistance to tuberculosis with a feeling of regret and with a sense that, while I may have struggled at times with unpardonable minutiae and repetition in making my position clear, I bring to an end a task incompletely performed and perhaps none too lucidly presented.

The nature of the subject has allowed nothing but the most meticulous and precise assembling and statement and restatement of evidence. At the same time, still more elementary treatment of it would have put upon me the necessity of a wealth of definition and description which would surely have enveloped leading outlines in an almost impenetrable haze. The phenomenon of resistance to tuberculosis is intricate; how complicated, how involved in faulty concepts, how cluttered up with semblances, only those who have given much time

to direct observation and reflection and brooding can appreciate. My main concern has been to search for a single and solid something which stands out plainly in resistance to tuberculosis and is at the same time not steeped in verbiage and is of itself not merely the trappings of resistance.

Yet the reaction of tissues, native, acquired, fixed or modified, is not the really fundamental thing in resistance. I have tried to lay bare in and through what process resistance works, and rises and falls. But tissue cells are the pieces through which the motive forces work, and I have said very little about fibroblasts and endothelium and leucocytes, lymphocytes, mononuclears, and so on; and it will no doubt some day be found that their interaction and relative weights are perhaps much more involved than the grosser tissue reactions which they bring about—in proliferation and exudation, in fibrosis and necrosis. Still further in the future lies the complete and comprehensible demonstration of the energies, the biochemical and biophysical impulsions and repulsions which set all the cells into play. And beneath all is life—whatever its essence may be.

All this goes into the making of resistance—resistance revealed to us in the crude yet unequivocal circumstance that the natural history of tuberculous infection is never exactly the same in any two animals.

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